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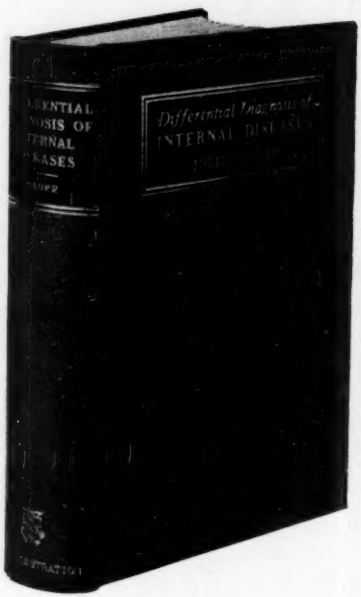

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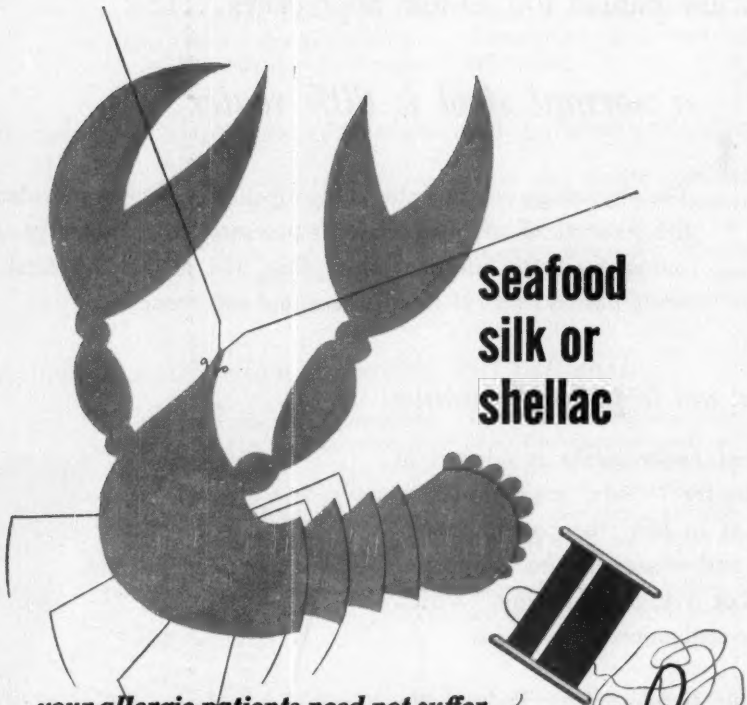

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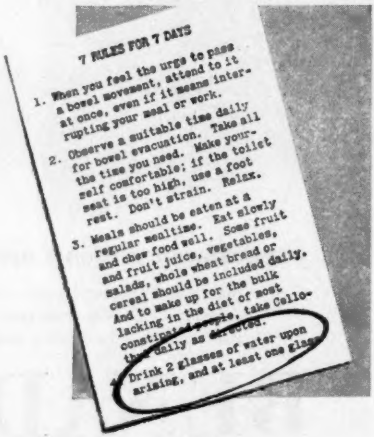
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1. Gray, H. and Tainter, M. L.: Am. J. Digest. Dis. 8:130, 1941.
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5. Council on Pharmacy and Chemistry: J.A.M.A. 143:897, 1950.

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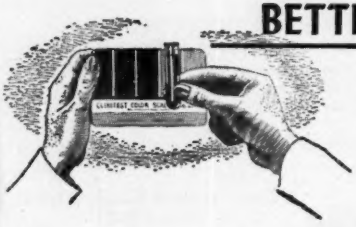

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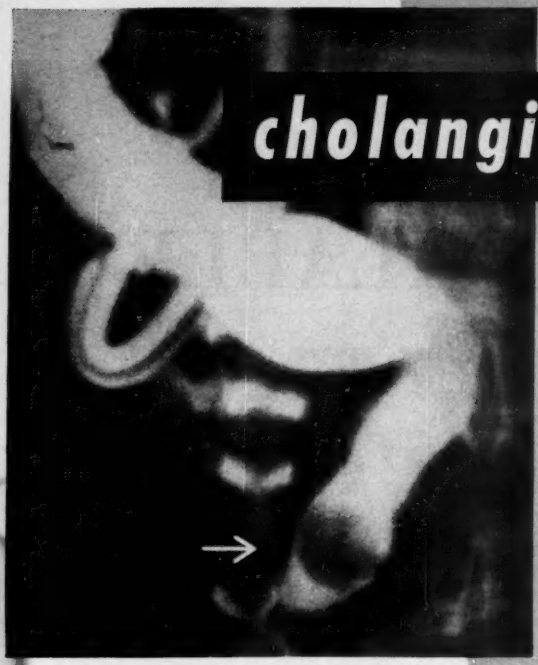

Cholangiogram with Diodrast 35% showing stone in distal end of common duct. Illustration, courtesy of Dr. J. Buckstein, author of "The Digestive Tract in Roentgenology" (Lippincott, 1948) in which a whole chapter is devoted to this procedure.

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PENICILLIN TREATMENT OF INFECTIOUS MONONUCLEOSIS

Comparison of Effects in Ninety-Nine Patients With and in Sixty-Seven Patients Without Penicillin Therapy

T. BENNIKE, M.D.
COPENHAGEN, DENMARK

DURING recent years, infectious mononucleosis has become increasingly prominent among the acute infections of the throat, probably primarily because of more frequent recognition of the disease, but perhaps also because of its increasing frequency.[1] This development naturally gives rise to the question of effective therapy, but, unfortunately, this does not yet appear to have been found. Since definite knowledge of the causation of the disease is still not available one must depend on empirical results in the field of therapy; therefore, it may be of interest to see how the disease is influenced by the new antibiotics.

The literature contains only scanty information on the subject, and this is often based on single cases or on very few observations. In regard to the effect of penicillin, opinions differ.[2] In those cases in which some improvement was thought to have occurred,[3] it seemed chiefly directed toward the accompanying tonsillitis,

This work was carried out with support from the National Danish Association Against Rheumatic Diseases.

From the Epidemic Hospital, Blegdams Hospital, Copenhagen, Denmark (Chief Physician, Prof. H. C. A. Lassen, M.D.).

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which was interpreted as a secondary bacterial complication. Good results were also said to have been obtained with one of the newest antibiotics, aureomycin, which is of particular significance because of its influence on certain viral infections.[4] On the other hand, however, such effects have also been denied.[5]

Experience up to now at Blegdams Hospital, where a total of nine patients with mononucleosis has been treated with aureomycin, has not shown any uniform result, but no "dramatic response" has occurred. Two patients, who had been treated a short time only, died.

It should be mentioned in this connection that earlier investigations (some from this hospital) have indicated a favorable effect from treatment with mononucleosis convalescent serum.[6] Subsequent experiences, however, have not borne out the primary expectations for this therapeutic agent, and practical difficulties have also been encountered in its procurement.

Of interest is a recent account from Bower and his associates of the good effect of treatment of mononucleosis with gamma globulin,[2b] though the series is too small to permit more extensive conclusions.

The aim of the present work, parallel to giving an account of the effect of penicillin in a large series of patients with tonsillitis,[7] has been to examine the influence of penicillin treatment on the course of infectious mononucleosis by comparison of a penicillin-treated group with a simultaneous control group not given penicillin. The work illustrates also certain characteristic trends in the occurrence of the disease in recent times.

MATERIAL AND METHODS

During the period October 1948 to July 1949, a total of 835 patients was admitted to the Epidemic Hospital, Blegdams Hospital, Copenhagen, with symptoms of acute tonsillitis. Closer examination revealed infectious mononucleosis in 166 (20 per cent) of the patients.

This diagnosis was based on the usual clinical and hematological criteria,[8] leukocyte and differential counts having been made for all patients at least twice during their stay in hospital. The Paul-Bunnell agglutination test was performed on 153 patients (92 per cent), this being supplemented by the absorption test of Davidsohn in all patients with titers above or equal to 1:32.[8a] Furthermore, urine examinations, including microscopy, measurements of hemoglobin

4. Lyons.[2c] Spink and Yow.[2e]

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8a. The serologic tests were carried out at the State Serum Institute by Dr. Martin Kristensen.

percentage and blood pressure readings were carried out on all patients, in addition to the taking of blood samples (usually one week after admission) for determination of sedimentation rate, Wassermann reaction and antistreptolysin titer. Electrocardiograms were made twice during the stay in the hospital. Swabs for hemolytic streptococci were taken daily from all patients for at least six days.

All tests were repeated at the follow-up examination one month later.

The patients were admitted to a "penicillin ward" and a "control ward," each of which received patients on alternate days, though patients who had received penicillin treatment before admission were chiefly placed in the "penicillin ward."

The two wards consisted of small rooms, and the patients admitted on different days were kept apart as much as possible; unfortunately, it was not possible to prevent relatives from visiting the rooms.

Patients in the penicillin group received the hospital's standard treatment: Adults received 150,000 units of ordinary soluble sodium salt of penicillin intramuscularly twice daily for six days, and children between 5 and 15 years of age received 120,000 units twice daily, those between 1 and 5 years of age were given 90,000 units twice daily and those under 1 year old received 60,000 units twice daily.

The patients in the control group were treated symptomatically; none was given salicylates.

The 166 patients comprised 87 males (52 per cent) and 79 females (48 per cent). Approximately half the patients had been treated with penicillin (30 patients) or sulfonamide preparations (26 patients) before admission, and 13 had received both. However, as far as the dose was concerned, the treatment had been insufficient in approximately half the patients, according to the criteria for treatment of, for example, pneumonia. Special examination of the course of the disease in the patients who had not received penicillin treatment previously showed no definite difference from that in the others; therefore, it was not considered necessary to exclude those patients who had been treated with penicillin before their admission to the hospital.

Thus, the series can be divided into a penicillin-treated group of 99 patients and a control group of 67 patients. The age and sex distribution was practically the same in the two groups.

On account of the special selection of the material, this series includes almost exclusively the anginose form of mononucleosis, which is by far the most frequent manifestation of the disease in this country.

RESULTS

Exudates on the tonsils were observed in nearly all the patients (97 and 96 per cent) in both groups. The exudates extended to the pharyngeal wall in nine of the penicillin-treated patients and in four of the control patients; thus, the diagnosis on admission was in many cases diphtheria.

Swabs for hemolytic streptococci taken from the throats of all patients during the treatment period were positive in 21 per cent of the total series, in 27 per cent of the controls and in 17 per cent of the penicillin-treated group, from whom swabs were taken only once before treatment was begun. After the first swab taking, there were 15 and 10 per cent positive reactions among the treated and control groups, respectively. Nearly all the streptococci belonged to Lancefield's group A, and the types were no different from those found in a series with acute tonsillitis examined simultaneously.

As in the patients with tonsillitis, the streptococci disappeared rapidly during the penicillin treatment and were not demonstrable after the third day, whereas in over three quarters of the controls the streptococci disappeared later than the third day. Among neither the penicillin-treated patients nor the controls were streptococci demonstrable on discharge from the hospital.

Examination of both groups shortly after admission showed a leukocyte count of over 10,000 per cubic millimeter in two thirds of the patients and of over 20,000

(maximum, 26,100) in only three, with characteristic mononucleosis and more or less pronounced granulocytopenia. In three of the patients the disease started with leukopenia (i. e., values below 4,000 cells per cubic millimeter), which in one case was as low as 2,500 cells per cubic millimeter. In less than 10 per cent of the patients in both groups slight eosinophilia (limit 400 eosinophils per cubic millimeter) was demonstrable during the disease; in 3 per cent this already was apparent on admission.

The sedimentation rate on discharge was below 20 mm. per hour in 57 per cent of the patients, with no difference in the two groups.

The Paul-Bunnell reaction, which was determined for 153 patients (92 per cent) after one week's stay in hospital, was positive in two thirds of the patients (63.5 per cent in the penicillin group and 68 per cent in the control group). However, among patients over 10 years of age only (63 per cent of the series), the reaction was positive in 84 per cent, as against 32 per cent among the children 10 years of age and below (fig. 1).

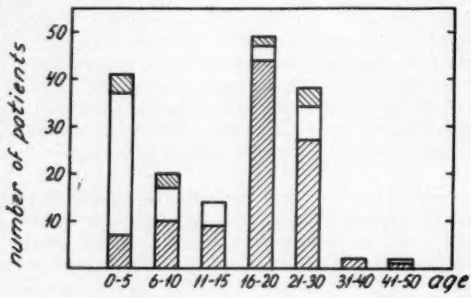

Fig. 1.—Age distribution and occurrence of Paul-Bunnell reactions among 166 patients with infectious mononucleosis. Right to left cross hatching indicates reaction was positive; white spaces indicate reaction was negative, and left to right cross hatching indicates test was not carried out.

Only in one case was a transient false positive Wassermann reaction found, which had practically disappeared at the examination one month later.

CLINICAL COURSE

Duration of fever can be seen from figure 2, which shows the practically uniform course in the two groups. One fifth of the patients were afebrile after two days' stay in hospital, independent of treatment, while 17 and 8 per cent of the treated and control groups, respectively, had fever for more than seven days. A calculation of the average duration of fever shows 4.7 days for the penicillin-treated group and 3.9 days for the control group.

Comparison of the temperature curves for the patients above and below 10 years of age does not permit any definite conclusions because of the small number involved, but a convincing penicillin effect was not observed in any of the age groups.

Disappearance of the exudates also seemed to proceed quite independent of treatment. It is peculiar that the number of patients with sore throat for over six

days in the penicillin-treated group (39 per cent) was almost double that in the control group (22 per cent).

The sore throat in the acute phase was also completely unaffected by penicillin treatment, with 25 and 20 per cent in the penicillin-treated group and control group, respectively, free from pain after two days. The fact that there were only five (5 per cent) patients with pain for more than seven days among the penicillin-treated patients, as against seven (14 per cent) among the controls, is hardly an indication of any definite difference.

Separate examination of the 35 patients whose swabs showed hemolytic streptococci provided no basis for definite conclusions because of the small number of patients, though it possibly indicated a certain effect of penicillin treatment on the duration of fever and pain in this group.

The duration of the disease, judged by the length of stay in hospital, was no different in the two groups, in both of which the average stay in the hospital was 13.4 days.

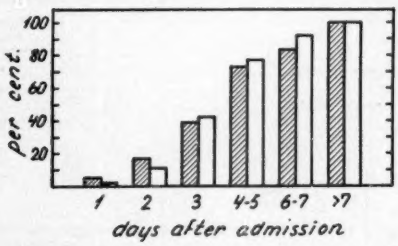

Fig. 2.—Percentage of patients afebrile on different days after admission to hospital among 99 penicillin-treated patients (shaded columns) and 66 controls (white columns) with infectious mononucleosis.

COMPLICATIONS

Table 1 shows the frequency of complications in the two groups during the acute phase of the disease. It is hardly possible, with the small numbers involved, to draw conclusions regarding the effect of penicillin in protecting against complications. It can be seen, however, that one case of otitis media and one case of phlegmonous tonsillitis occurred and among only the control patients.

Slight albuminuria and hematuria were seen in a few persons in both groups.

Penicillin treatment was instituted secondarily in a patient of the control group who had severe arthralgia the day after admission and later in another control patient with marked hematuria on admission. No occurrence of rheumatic fever or nephritis was observed during the disease.

Penicillin treatment had no effect on the course of the rare acute febrile "typhoid" form of mononucleosis, which occurred in seven of the penicillin-treated and in one of the control patients.

Slight hemorrhagic diathesis was seen in two of the penicillin-treated group and in one of the control patients, in the form of severe bleeding from ulcerations in the throat, repeated epistaxis (seven times during stay in hospital) and petechiae in the skin. In two of these patients reduced capillary resistance was found by stasis

test, and one of the patients, in addition, had prolonged prothrombin time (45 seconds as against 22 seconds for the control sample by the one stage method), while the other tests (bleeding time, coagulation time and thrombocyte count) showed normal values.

In a further two patients, who had otherwise no bleeding tendency, it was found that initially in the disease one had slight thrombocytopenia (55,000 thrombocytes per cubic millimeter) and one had prolonged prothrombin time (58 seconds as against 26 seconds for the control specimen).

Slight anemia occurred during the disease in 15 per cent of both groups. In most cases this had disappeared at the time of the follow-up examination.

Severe icterus was not encountered in any of the patients, but one of the control patients showed an icterus index of 12, which fell quickly to normal value.

A noncharacteristic exanthem was observed in 20 per cent of the total series, with 11 per cent in the penicillin-treated patients and 30 per cent in the controls.

TABLE 1.—*Complications During the Course of Infectious Mononucleosis*

	Penicillin Group (99 Patients)	Control Group (67 Patients)
Secondary temperature increase	8	11
Secondary adenitis	0	1
Secondary phlegmonous tonsillitis	0	1
Otitis media	0	1
Albuminuria		
On admission	2	2
During treatment	3	1
Hematuria		
On admission	3	3 *
During treatment	1	1
Arthralgia	0	1 †
Electrocardiographic changes in T waves of lead I and/or II	7	3
Hemorrhagic diathesis	2	1
"Typhoid" course	7	1

* One patient received penicillin for secondary symptoms.
† The patient received penicillin for secondary symptoms.

This was noted in nearly all cases either on admission or shortly afterward. No relation to chemotherapy before admission, streptococcic findings or simultaneously occurring eosinophilia could be demonstrated.

The electrocardiographic changes occurring in the acute phase of the disease did not vary from those seen during ordinary tonsillitis [7] and, on the average, were of the same transitory asymptomatic character, without significant difference in the two groups. As in Thomsen's material,[8c] the principal changes occurred in the T waves, with depression or inversion in two or more deflections during the acute phase of the disease. This occurred in lead I and/or lead II in approximately 5 per cent of both groups, but transient increased negativity in lead III alone occurred in over one third of the patients, independent of treatment. Only in one patient, a child 6 years of age, were these changes seen again at an ambulatory examination one month after discharge. The patient, who otherwise was quite well, showed isoelectric T_1 and T_3 waves.

Apart from two patients with some cyanosis in the acute phase, the cardiac origin of which was doubtful, and one patient in whom extrasystoles were found, none showed clinical or stethoscopic signs of cardiac disease.

RESULTS OF FOLLOW-UP EXAMINATION

Six patients had to be excluded from the series because, after discharge from the hospital, they had received penicillin treatment on account of recidivity or complications or had had tonsillectomy performed (three patients). Nearly all the remaining patients (99 per cent) were examined from four to eight weeks after discharge, and the previously mentioned tests were carried out.

In only a few cases did otitis media, cervical adenitis and subfebrile conditions occur during convalescence, without any notable difference in the two groups (table 2). Acute tonsillitis during the first month after discharge occurred in 13 and 8 per cent of the treated and control patients, respectively.

A sedimentation rate of 20 mm. per hour or more was seen on follow-up examination in seven of the previously penicillin-treated patients and in one of the controls, without any apparent cause.

TABLE 2.—*Complications in First Month Following Discharge from Hospital After Infectious Mononucleosis*

	Penicillin Group (95 Patients)	Control Group (63 Patients)
Acute tonsillitis	12	5
Otitis media	1	1
Sinusitis	0	0
Cervical adenitis	0	1
Stomatitis	0	1
Arthralgia	2	1
Subfebrile condition	2	1
Sedimentation rate greater than or equal to 20 mm. per hour at follow-up examination	7	1

The antistreptolysin titer was determined for all patients on discharge. Higher values (≥ 200) were found in 14 per cent of the penicillin-treated patients and in 20 per cent of the controls, but in 40 per cent of control patients with positive cultures for Streptococcus.

Determination of antistreptolysin titer was made at the follow-up examination in 90 per cent of all the patients. Increases of over 50 per cent, to titers of 200 or more, were seen in 4 and 10 per cent of the treated and control patients, respectively, but in 30 per cent of the control patients with cultures positive for Streptococcus.

A positive Paul-Bunnell reaction was observed at the follow-up examination in 63 per cent of the patients who had shown a positive reaction during the disease, without definite difference between treated and control patients (66 and 58 per cent, respectively).

Lymphocytosis in excess of that physiological for the age was seen in two thirds of the penicillin-treated patients and in three quarters of the controls followed up. However, actual McKinlay cells were observed in only 15 per cent of both groups.

Penicillin treatment did not seem to have any influence on the convalescence fatigue so often occurring after mononucleosis, as about 20 per cent in both groups mentioned at the follow-up examination that they were extremely and unusually tired.

COMMENT

It is obvious from a study of the total material available that the age distribution among our patients is considerably different from that Thomsen reported for his material collected at the same hospital during the period 1927 to 1938 [8c] (see fig. 1). While only 15 per cent of his patients were in the age group of 10 years and below, this age group in our series comprised 37 per cent of all patients, with approximately 25 per cent 5 years of age or below. This fact can hardly be explained alone by the more difficult hematological diagnosis in small children, with their physiological lymphocytosis, which occasionally includes also cells of mononucleosis character.[9] It must certainly be due to a large extent to an actual increase of the disease in these age groups. This is not necessarily contradicted by the fact that the Paul-Bunnell test in patients below 10 years of age showed positive results in only one third (32 per cent) of the patients, while the reaction was positive in 84 per cent of those over 10 years of age, since other authors have found less frequent positive agglutination in children.[10]

The clinical course further makes it probable that these children did not have simple tonsillitis. Comparison with a simultaneous series of patients who had tonsillitis shows a more protracted course of elevation in temperature in children with mononucleosis than in those with tonsillitis.

In this connection it should be mentioned that there are still authors who regard the *"fièvre ganglionnaire"* of childhood as essentially different from the mononucleosis of adults.[9a]

A correspondingly high frequency of mononucleosis in children is also known from other series.[11] However, these cases have often been of an epidemic form of mononucleosis. It is still an unsettled question whether the sporadic cases are only the more pronounced manifestations of a disease the epidemic character of which is concealed by the many cases that proceed without symptoms.[12]

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9. (*a*) Chaptal, J., and Labraque-Bordenave, M.: A propos de quinze cas de fièvre ganglionnaire de l'enfant: Étude hématologique et sérologique, Sang **15**:531-538, 1942-1943. (*b*) Footnote 1*a*.

10. Bang, O., and Kristensen, M.: Clinical Investigations on Occurrence of Agglutinin of Sheep Blood Corpuscles (Heterophile Antisubstance) in Serum of Patients with Infectious Mononucleosis, Ugesk. f. læger **98**:1049-1054 (Oct. 29) 1936. Glanzmann, E., and Ottensooser, F.: Ueber die Vermehrung der Hammelblut-Agglutinine beim Drüsenfieber und den diagnostischen Wert dieser Heteroagglutination, Schweiz. med. Wchnschr. **65**:520-523 (June 8) 1935. Thomsen.[8c]

11. Guthrie, C. C., and Pessel, J. F.: An Epidemic of "Glandular Fever" in a Preparatory School for Boys, Am. J. Dis. Child. **29**:492-496 (April) 1925. Klemola, E.: Studies of Infectious Mononucleosis, Acta med. Scandinav. **127**:149-170, 1947. Nolan, R. A.: Report of So-Called Epidemic of Glandular Fever (Infectious Mononucleosis), U. S. Nav. M. Bull. **33**:479-483 (Oct. 1) 1935. Tidy, H. L., and Morley, E. B.: Glandular Fever, Brit. M. J. **1**:452 (March 26) 1921.

12. Bernstein.[8a] Footnote.[1a] Guthrie and Pessel.[11] Baldridge, C. W.; Rohner, F. J., and Hansmann, G. H.: Glandular Fever (Infectious Mononucleosis), Arch. Int. Med. **38**:413-448 (Oct.) 1926. Halcrow, J. P. A.; Owen, L. M., and Rodger, N. O.: Infectious Mononucleosis, with an Account of an Epidemic in an E. M. S. Hospital, Brit. M. J. **2**:443-447 (Oct. 9) 1943. Heyeraas, H.: Epidemiology of Infectious Mononucleosis, Nord. med. **35**:1495-1500 (July 11) 1947. Wechsler, H. F.; Rosenblum, A. H., and Sills, C. T.: Infectious Mononucleosis: Report of an Epidemic in an Army Post, Ann. Int. Med. **25**:113-133 (July); 236-265 (Aug.) 1946.

That the frequency of the disease as a whole has increased appears from the fact that the percentage of cases of mononucleosis among patients admitted to Blegdams Hospital for acute tonsillitis has increased from approximately 8 per cent in 1938 [sic] to 20 per cent in 1948-1949. This fact can hardly be explained alone by an increased interest in this disease.

CONCLUSIONS

In regard to the therapeutic result of penicillin treatment in the material available, it must be concluded that it has no effect on the clinical course of mononucleosis as such. On the other hand, penicillin has the effect of inhibiting the streptococci and, in consequence, presumably prevents complications in cases in which secondary bacterial infection occurs. As, however, such complications are seldom seen, penicillin treatment of infectious mononucleosis generally is hardly indicated.

SUMMARY

The diagnosis of infectious mononucleosis was made for 166 (20 per cent) of 835 patients admitted to the hospital with symptoms of acute tonsillitis. Of these, 99 were treated with penicillin given intramuscularly twice daily, while 67 control patients were not given such treatment. In 21 per cent of the entire series throat culture showed beta hemolytic streptococci group A.

Penicillin treatment had no effect on the duration of fever, presence of exudate or persistence of sore throat, and the average stay in hospital was the same in both groups (13.4 days).

Pyogenic complications (otitis media, phlegmonous tonsillitis) occurred in a few of the control patients.

Slight electrocardiographic changes occurred with equal frequency in the two groups.

At a follow-up examination four to eight weeks after discharge from the hospital, the course of convalescence and the antistreptolysin reaction were compared in the two groups.

Finally, the incidence of the disease according to age is discussed. From a series with sporadically occurring infectious mononucleosis, it is extraordinary that a high percentage of patients was in the age group of 10 years and below (37 per cent).

It is concluded that penicillin treatment is scarcely indicated in infectious mononucleosis generally, but that it probably has an effect in preventing complications in patients with secondary streptococcic infection.

COMBINED ADMINISTRATION OF DESOXYCORTICOSTERONE ACETATE AND ASCORBIC ACID

I. Clinical Results in Rheumatoid Arthritis and Laboratory Studies

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THE EFFECTS of therapy with pituitary adrenocorticotropic hormone (ACTH) and cortisone in rheumatoid arthritis have stimulated clinical trials of more readily available steroids and related compounds. Of this group, desoxycorticosterone acetate combined with ascorbic acid has been introduced relatively recently and because of its availability has already been tried in many centers throughout the world.

The first report of the use of combined desoxycorticosterone acetate and ascorbic acid was the preliminary communication of Lewin and Wassén [1] in *The Lancet* of Nov. 26, 1949. The Swedish workers treated six women and three men with rheumatoid arthritis by administering 5 mg. of desoxycorticosterone acetate intramuscularly, followed within five minutes by the giving of 1,000 mg. of ascorbic acid intravenously. In all nine of their patients prompt improvement was reported, with almost complete subsidence of pain and definite increase in joint motility within 15 to 30 minutes. Improvement persisted from two to 24 hours and occurred in cases of long standing, as well as in those of more recent onset.

The numerous communications on the subject which have appeared since have been remarkable for the diversity of the clinical results reported. Opinions regarding the value of combined therapy in rheumatoid arthritis are divided between favorable [2] and adverse.[3] There have also been reports of improvement in post-traumatic stiffness and pain, ankylosing spondylitis and mental disorders.

From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

1. Lewin, E., and Wassén, E.: Effect of Combined Injections of Deoxycortone Acetate and Ascorbic Acid on Rheumatoid Arthritis, Lancet **2**:993 (Nov. 26) 1949.

2. LeVay, D., and Loxton, G. E.: Deoxycortone Acetate and Ascorbic Acid in Treatment of Rheumatoid Arthritis, Lancet **2**:1134 (Dec. 17) 1949. Fox, W. W.: Deoxycortone Acetate and Ascorbic Acid in Rheumatoid Arthritis, Letters to the Editor, ibid. **2**:1156 (Dec. 17) 1949. Loxton, G. E., and LeVay, D.: Deoxycortone Acetate and Ascorbic Acid in Rheumatoid Arthritis, Letters to the Editor, ibid. **2**:1204 (Dec. 24) 1949. Douthwaite, A. H.: Deoxycortone Acetate and Ascorbic Acid in Rheumatoid Arthritis, Letters to the Editor, ibid. **2**:1244 (Dec. 31)

CLINICAL OBSERVATIONS IN RHEUMATOID ARTHRITIS

Material.—Our experience with combined desoxycorticosterone acetate and ascorbic acid therapy in rheumatoid disease includes 20 cases of peripheral rheumatoid arthritis and three cases of spondylitis. There were 17 women and 6 men, ranging in age from 17 to 71.

In general, these cases were characterized by chronicity and proved refractoriness to therapy, the majority of patients having been treated prior to combined therapy with one or several of the following: physical therapy, gold preparations, blood transfusion, large doses of neoarsphenamine, epinephrine intravenously and fever shock therapy, using typhoid vaccine or pyrogenic protein-free extract of Pseudomonas organisms (pyromen®). In almost all instances the patients were referred for a trial of combined therapy only after other available therapeutic approaches had failed.

Method of Treatment.—The technic of Lewin and Wassén was followed. Five milligrams of desoxycorticosterone was injected intramuscularly into the lateral aspect of the thigh, and this was followed within two to 10 minutes by intravenous injection of 1,000 mg. of ascorbic acid in 5 or 10 cc. of buffered solution.

Because the first patient showed rather dramatic improvement following one dose, it was our early impression that a single dose would indicate whether a given patient was likely to benefit. Thus, seven of the patients who showed little or no improvement received only one treatment, which, judging from later experience, might be regarded as an inadequate trial of the therapy. Another patient who showed no response received only two treatments. The remaining 16 received four or more treatments at intervals of from one every 12 hours to one every four days. An effort was made to avoid "suggestion" in that patients were not told what medicine

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3. Kellgren, J. H.: Deoxycortone Acetate and Ascorbic Acid in Rheumatoid Arthritis, Letters to the Editor, Lancet **2**:1108 (Dec. 10) 1949. Hartfall, S. J., and Harris, R.: Deoxycortone Acetate and Ascorbic Acid in Rheumatoid Arthritis, Letters to the Editor, ibid. **2**:1202 (Dec. 24) 1949. Hart, V. L., and Starer, F.: Deoxycortone Acetate and Ascorbic Acid in Rheumatoid Arthritis, Letters to the Editor, ibid. **2**:1203 (Dec. 24) 1949. Spies, T. D.; DeMaeyer, E.; Stone, R. E., and Niedermeier, W.: Deoxycortone with Ascorbic Acid Versus Adrenocorticotropic Hormone in Rheumatoid Arthritis, ibid. **2**:1219 (Dec. 31) 1949. Fletcher, E.; Lush, B.; Buchan, J. F., and Wolff, S.: Deoxycortone Acetate and Ascorbic Acid in Rheumatoid Arthritis, Letters to the Editor, ibid. **1**:94 (Jan. 14) 1950. Talaat, S. M.: Treatment of Rheumatoid Arthritis, Letters to the Editor, ibid. **1**:326 (Feb. 18) 1950. Ballabio, B. C., and Sala, G.: Research on Arthritis Treatment, Letters to the Editor, ibid. **1**:644 (April 1) 1950. Geiringer, E.: Research on Arthritis Treatment, Letters to the Editor, ibid. **1**:643 (April 1) 1950. Kersley, G. D.; Mandel, L., and Jeffrey, M. R.: Steroid Therapy in Rheumatoid Arthritis, ibid. **1**:703 (April 15) 1950. Currie, J. P., and Will, G.: Treatment of Rheumatoid Arthritis with Deoxycortone and Vitamin C, ibid. **1**:708 (April 15) 1950. Copeman, W. S. C., and others: Deoxycortone with Ascorbic Acid in Rheumatoid Arthritis, Letters to the Editor, ibid. **1**:830 (April 29) 1950. Bywaters, E. G. L.; Dixon, A. S., and Wild, J. B.: Deoxycortone and Ascorbic Acid in Treatment of Rheumatoid Arthritis, ibid. **1**:951 (May 20) 1950.

they were receiving, what results might be hoped for or when they might be expected. All patients were under the observation of one of us, but many of the treatments were carried out by other members of the staff.

Results of Clinical Trials.—Of the 16 patients who received more than two treatments, nine showed definite subjective or objective improvement (table 1). In three of these patients moderate to pronounced improvement was reported within 30 to 60 minutes after the first dose, while in the remainder improvement was not noted until the third or fourth doses.

TABLE 1.—*Clinical Response in Twenty-Three Patients with Rheumatoid Arthritis Treated with Combined Desoxycorticosterone Acetate (DCA) and Ascorbic Acid*

Case No.	Sex	Age	Treatment Schedule	Period of Observation, Days	Improvement and Duration	
					Subjective	Objective
1	F	68	St.* every 4 days, 4 times	150	+++ (7 days) 0 (later)	+++ (7 days) 0 (later)
2	F	53	St. once	7	+ (5 days)	0
3	F	51	St. once	1	+	0
4	F	55	St. once	1	0	0
5	F	38	St. every 4 days, 4 times	30	+++ (30 days)	++ (30 days)
6	F	60	St. once	1	+	0
7	F	33	St. every day, 6 times; every 5 days, 12 times; DCA pellets 450 mg. + ascorbic acid i. m. 500 mg. every 2 days for 2 months	120	++ (120 days)	+ (120 days)
8	F	49	St. once	1	0	0
9	M	62	St. twice	8	0	0
10	M	52	St. once	2	0	0
11	F	42	St. every day, 7 times; every 2 days, 9 times; DCA pellets 450 mg. + ascorbic acid i. m. 500 mg. every 2 days	120	++ (120 days)	++ (120 days)
12	F	35	St. every day, 12 times; every 7 days, 12 times	80	++ (14 days) 0 (later)	+ (14 days) 0 (later)
13	F	42	St. once	7	0	0
14	F	71	St. twice a day for 3 days	10	0	0
15	F	51	St. twice a day for 3 days	10	0	0
16	M	56	St. 8 times in 5 days	7	0	0
17	F	60	St. every day, 6 times; every 3 days, 5 times	22	++ (22 days)	++ (22 days)
18	M	64	St. every day, 7 times	20	0	0
19	F	62	St. every 2 days, 5 times; twice a week, 14 times	50	+++ (50 days)	++ (50 days)
20	M	58	St. every day, 5 times	6	0	0
21 †	M	35	St. 3 times in 5 days; 1 or 2 per week for 9 weeks; later DCA pellets 450 mg. + ascorbic acid i. m. 500 mg. every day	150	++ (150 days)	++ (150 days)
22 †	F	23	St. 7 times in 12 days	30	0	0
23 †	F	19	St. twice a day for 5 days	30	++ (30 days)	++ (30 days)

* Standard technic.[1]
† Rheumatoid spondylitis.

Brief protocols on these improved patients will be outlined, inasmuch as they may indicate explanation for the therapeutic responses.

CASE 1.—A 68 year old woman had rheumatoid arthritis for several years with deformities, pain, tenderness and limitation of motion of the joints of hands, elbows, hips, knees and ankles. Over a period of years preceding treatment with desoxycorticosterone acetate and ascorbic acid, she had received a variety of nonspecific therapies.

Twenty minutes after the initial combined therapy she reported less pain and stiffness in general, and 30 minutes afterward her gait and ability to climb stairs were remarkably improved. She could close both hands tightly for the first time in months and was completely free from pain. This improvement was maintained for about 24 hours. During the second and third days her condition returned to about that which existed before treatment, but by the fourth day it was worse than ever. A second treatment produced prompt and remarkable improvement.

An average stride increased from 10 to 15¾ inches (24 to 32 cm.) at the end of 30 minutes, and the painless range of straight leg raising increased by 26 degrees on the right and 70 degrees on the left. The patient remained free of pain for 48 hours. On the next visit injections of sterile isotonic sodium chloride solution were substituted without the patient's knowledge. She reported slight subjective improvement, but no objective change could be demonstrated. The third trial was followed by less improvement than the first and second treatments, and no clinical response followed the fourth treatment. Several months later this patient was admitted to the hospital, placed on a diet containing less than 0.5 Gm. of sodium per day and given ascorbic acid intravenously at the rate of 2,000 mg. per day for several days. This regimen not only failed to produce clinical improvement, but the arthritic manifestations became severer, and, in addition, salt depletion symptoms developed. When sodium chloride was again added to the diet, the patient gained 6½ pounds (3 Kg.) in three days. During the last three days of hospitalization, desoxycorticosterone acetate was substituted for the placebo injections of sesame oil which had been given along with the ascorbic acid and the patient showed only equivocal improvement.

Comment.—This patient showed remarkable and dramatic improvement following the first few injections of desoxycorticosterone acetate and ascorbic acid. After the third treatment, however, no further response was obtained in spite of manipulation of salt intake devised to test the possible influence of sodium balance. The net gain from the use of desoxycorticosterone acetate and ascorbic acid in this patient was nil, and she has resumed physical therapy. Prolonged association with the patient indicated the possibility that the initial improvement, remarkable as it was, could be attributable to psychotherapeutics.

CASE 5.—A woman, aged 38, had rheumatoid arthritis of six months' duration which affected wrists, elbows, shoulders and hands. When desoxycorticosterone acetate and ascorbic acid treatment was tried, the patient had been in the hospital for several weeks and had received in succession typhoid vaccine intravenously, neoarsphenamine and stellate ganglion blocks without benefit. Forty-five minutes after combined therapy she reported a general "looseness," increased joint mobility and decreased pain. She could then walk and move about freely in bed without pain. That night she slept well without sedatives for the first time in weeks, and her roommates noted that she turned in her sleep without groaning as she had previously done. The treatment was repeated at intervals of four days until she left the hospital 2½ weeks later, and the over-all improvement was maintained during this time.

Comment.—This response could not be readily attributed to psychotherapeutics because the patient's symptoms had been demonstrated previously to be refractory to other types of therapy.

CASE 7.—A 33 year old woman had moderately severe rheumatoid arthritis for 14 months, which affected principally the knees, ankles, feet, wrists and hands. She previously received blood transfusions, physical therapy, courses of intravenous treatment with epinephrine, typhoid vaccine and neoarsphenamine. For three months prior to and during the trial of combined therapy she received gold sodium thiomalate in an average weekly dose of 25 mg.

After three daily combined treatments, the range of motion of the fingers and wrists was increased considerably. There was less pain in all affected joints, and gait improved. Further gains of function occurred during the next nine weeks, during which she received two treatments per week as an outpatient. If treatment was omitted for more than a week, pain and stiffness returned in all affected joints. Improvement was maintained on dose levels of desoxycorticosterone acetate totaling 10 mg. per week and ascorbic acid intramuscularly in doses of 500 mg. every second day. In order to facilitate long term management, pellets of desoxycorticosterone acetate totaling 450 mg. were implanted subcutaneously, and thereafter ascorbic acid was given by a member of the family in intramuscular injections of 500 mg. every day, and later every other day. After 10 weeks the patient continued to show steady improvement with respect to appetite, energy and endurance and had gained 10 pounds (4.5 Kg.) without demonstrable edema. The sedimentation rate remained rapid and was essentially unaltered by therapy.

Comment.—It is possible that improvement in this patient could represent a delayed response to the preceding gold therapy. However, the sharp onset of improvement coincided with the exhibition of desoxycorticosterone acetate and ascorbic acid.

CASE 11.—This patient was a 42 year old woman who had rheumatoid arthritis of 16 years' duration, with particularly severe symptoms in the preceding year. The patient was admitted to Cleveland Clinic Hospital with pain, swelling, redness, limitation of movement in both knees,

elbows, wrists, hands and ankles and particularly severe involvement of the right hip. Without the patient's knowledge 25 mg. of cortisone acetate was given, and within two hours decreased pain and increased mobility were noted in all joints except the right hip. This partial remission was maintained for about 48 hours, but at the end of the third day symptoms approached pretreatment severity. At this time combined therapy was tried, and some improvement was reported after three daily treatments. After six days improvement was considerable, and the elbows, wrists, hands and ankles were less swollen, tender and painful. Swelling continued to subside in joints that had been enlarged for years. After two weeks the knuckles were so reduced in size that a wedding ring, which for several years could not be removed, virtually fell off the dependent finger. The only affected joint which did not respond was the right hip. The patient had been taking up to 5 grains (0.32 Gm.) of codeine per day for relief of pain, and, although an element of addiction had undoubtedly developed, it became possible to reduce the intake to less than 2 grains (0.13 Gm.) per day. Treatments were continued every two to three days from the second to the fourth week, and then 450 mg. of desoxycorticosterone acetate in pellets was implanted subcutaneously. The patient was instructed to take daily intramuscular injections of 500 mg. of ascorbic acid at home. Although the other involved joints continually improved, the process in the right hip showed relentless progression by clinical and roentgenographic criteria. Four months after the initiation of therapy with desoxycorticosterone acetate and ascorbic acid, there was no evidence of active arthritis in any joint but the right hip. At the patient's insistence, a trial of cortisone was carried out while the pellets of desoxycorticosterone acetate remained in place and the ascorbic acid injections were continued. No improvement occurred with placebo injections or with cortisone in dose levels of less than 100 mg. per day. However, with daily doses of 100 to 150 mg. of cortisone acetate, the right hip joint became much less painful and improved locomotion was possible. Cortisone administration is to be continued for several weeks in an effort to halt the destructive process in the right hip.

Comment.—It is difficult to explain the progression of destructive joint disease in one hip while chronically involved joints elsewhere were undergoing a remarkable remission. There may have been a spontaneous remission, or combined therapy may have effected a remission in joints previously demonstrated to be treatment-responsive by the use of a small dose of cortisone. On the other hand, there might have been aggravation of the process in the right hip, which then became the locus of a stress sufficient to activate the pituitary-adrenal system and bring about elaboration of endogenous corticoids to influence favorably the less actively involved joints.

CASE 12.—This was a case of rheumatoid arthritis of four years' duration in a woman of 35, involving nearly all peripheral joints. Swelling and stiffness of wrists and hands were particularly troublesome. During the first 15 days in the hospital the patient received 11 daily injections of pyromen,® and, although these treatments brought about sharp decreases in circulating eosinophils (54 to 73 per cent), there was little or no clinical improvement.

Two days after the last pyromen® treatment desoxycorticosterone acetate and ascorbic acid therapy was started. Definite subjective and objective improvement was reported three hours later in that the hands were less stiff and painful. She received nine treatments in six days, with improvement continuing to the point where all pain and visible swelling and redness had left the wrist and hand joints. The skin was no longer cool and sweaty. The patient had slight ankle edema on the sixth day, and the number of treatments was reduced to one per day. As time went on, less and less relief was obtained, and, finally, after 12 weeks and 25 combined injections, treatment was discontinued as it was no longer influencing the symptoms.

Comment.—This patient was regarded as neurotic and in addition showed manifestations of a labile vasomotor system, including Raynaud's phenomenon. Although efforts were made to avoid "suggestion," the improvement in this patient may be attributable to psychogenic alteration in vasomotor control.

CASE 17.—A woman, 60 years old, had rheumatoid arthritis of seven years' duration with several atypical features suggesting a gouty element. In the past year there was continuous and more typically rheumatoid involvement of knees, ankles, shoulders and hands, and no definite relief had followed the use of colchicine, arsphenamine intravenously, typhoid vaccine or blood transfusion or four months of therapy with gold salts. The last was discontinued just prior to the trial of combined therapy. After administration of desoxycorticosterone acetate and ascorbic acid, appreciable decrease in pain occurred within a few hours, which at first was regarded as an

ordinary fluctuation in symptoms. However, when improvement continued in spite of bad weather conditions and she became able to carry out formerly impossible maneuvers (such as climbing steps without the use of a hand rail and rising unaided from a kneeling position), she regarded the remission as extraordinary. The former swollen, red, painful metacarpophalangeal joints became normal appearing, and full flexion of the fingers became possible after the sixth daily treatment. Treatments were continued at intervals of two per week for several weeks. Improvement was, in general, maintained, and the patient resumed activities, such as gardening, which were previously impossible because of the limitations imposed by pain and restricted joint motility.

Comment.—Definite subjective and objective improvement followed immediately on the use of desoxycorticosterone acetate and ascorbic acid in this patient. After the first few weeks, however, treatment appeared to become less effective, until latterly it was doubtful whether combined therapy or the physical therapy given concurrently was maintaining the remission.

CASE 19.—A woman, 62 years of age, had moderately severe rheumatoid arthritis of 15 years' duration, with a recent exacerbation for seven months. Both shoulders and hands, the left hip and, particularly, both knees and ankles were swollen, hot and extremely tender. After the first treatment, the patient reported that she could bear weight with less discomfort and was able to sleep better. After the second daily treatment, there was increased mobility in the hands and the left knee showed a gain of 60 degrees of flexion. After the fourth treatment, the right knee had gained 60 degrees of active flexion, both hands could be clenched tightly and she could descend stairs forward, maneuvers which had been impossible in the preceding nine months. The hands, knees, ankles and feet showed rapid regression of heat, redness and swelling, so that shoes, formerly discarded because of swelling and tenderness, were being worn. On a schedule of two treatments per week there has been continued improvement. The erythrocyte sedimentation rate has remained rapid, and the involved joints continue to show a disposition to flare up briefly following any strenuous activity or trauma.

Comment.—A period of steadily increasing subjective and objective improvement began within a day or two after the exhibition of desoxycorticosterone acetate and ascorbic acid in this patient. Particularly gratifying to the patient has been the relief from aching pain at night, permitting effective sleep.

CASE 21.—A 37 year old baker had advanced rheumatoid spondylitis and arthritis of 10 years' duration. In the month prior to the trial of combined therapy there had been an exacerbation, with acute involvement of both hips. The legs were immobilized in a semiflexed position on pillows to reduce pain, and the patient feared to be moved or handled. The first injections of desoxycorticosterone acetate and ascorbic acid were followed promptly by a diminution of pain which permitted him in 30 minutes to straighten the leg and move about in bed. He slept unusually well. The next morning there was only slight pain in one hip on standing. Physical therapy, previously impossible because of pain, was now commenced and probably contributed largely to the continued gradual improvement. After nine weeks the injections were discontinued, but the patient reported definite worsening of symptoms. Therefore, 2½ weeks later, 450 mg. of desoxycorticosterone acetate in pellets was implanted subcutaneously, and the patient has taken 500 mg. of ascorbic acid intramuscularly daily for the three months since that time. His symptoms have continued to improve gradually, and rehabilitation training is under way.

Comment.—It has appeared at times, as in the case previously described, that desoxycorticosterone acetate and ascorbic acid can bring about sufficient relief of pain to permit institution of effective physical therapy.

CASE 23.—A 19 year old Negro girl had had intermittent attacks of peripheral arthritis for seven years. The last attack began 1½ years ago and involved principally spinal, sacroiliac and hip joints. She was given combined therapy twice a day for five days and obtained considerable relief from pain.

Comment.—This was another case in which Dr. Shelby G. Gamble, Director of Physical Medicine, noted that the exhibition of desoxycorticosterone acetate and ascorbic acid permitted adequate physical therapy to be carried out. The definite gains in joint function which have ensued are probably attributable to the physical therapy.

LABORATORY STUDIES ON PATIENTS AND ON NORMAL PERSONS

Certain cytological and metabolic studies were carried out in an attempt to determine whether desoxycorticosterone acetate and ascorbic acid in combination could possibly produce a cortisone-like action or potentiate endogenous corticoid activity.

Circulating Eosinophils.—A prompt decrease in circulating eosinophils has come to be regarded as a convenient, if not entirely specific, indicator of glucocorticoid activity. Therefore, the blood eosinpohil count was determined prior to and four hours after the initial injection of desoxycorticosterone acetate and ascorbic acid in several patients (table 2).

There is no relationship apparent between the clinical response and the eosinopenic response in this group. The injections per se probably initiated a mild alarm reaction, which is known to be accompanied with eosinopenia provided the hypo-

TABLE 2.—*Blood Eosinophil Response After Injection of Desoxycorticosterone Acetate and Ascorbic Acid*

Age	Sex	Diagnosis	Response to Treatment		Eosinophils/Cu. Mm.		
			Subjective	Objective	Before Rx	4 Hr. After	% Change
55	F	Rheumatoid arthritis	0	0	194	181	— 7
38	F	Rheumatoid arthritis	+++	++	100	88	—12
33	F	Rheumatoid arthritis	++	+	156	150	— 4
35	F	Rheumatoid arthritis	++	+	169	231	+37
68	F	Rheumatoid arthritis	+++	+++	100	44	—56
56	M	Rheumatoid arthritis, atypical	0	0	219	269	+12
42	F	Rheumatoid arthritis	+++	++	200	206	+ 3
70	M	Rheumatoid arthritis, atypical	0	0	150	81	—46
				Average	161		— 9
23	F	Rheumatoid spondylitis	0	0	69	34	—52
35	M	Rheumatoid spondylitis	+++	+	38	31	—16
17	F	Lupus erythematosus	0	0	38	50	+30
28	F	Scleroderma	0	0	156	106	—32

thalamopituitary-adrenal axis is intact. This explanation is favored by the following observations: 1. Intravenous injection of 1,000 mg. of ascorbic acid without desoxycorticosterone acetate into six normal persons resulted in eosinophil decreases averaging 35 per cent (range, — 16 to — 64 per cent). 2. Following combined injection of desoxycorticosterone acetate and ascorbic acid to four patients with Addison's disease, the eosinophil counts changed by — 18, + 53 and — 5 per cent, respectively.

The eosinopenic response of the rheumatoid group (average, — 9 per cent; range, — 56 to + 37 per cent) was appreciably less than that which followed combined injections of desoxycorticosterone acetate and ascorbic acid into 11 normal controls in whom the average decrease was — 32 per cent, with a range from — 57 to + 4 per cent. The average pretreatment eosinophil count tended to be lower in the rheumatoid group (average, 161; range, 100 to 219 per cubic millimeter) than in the normal subjects (average, 239; range, 94 to 312 per cubic millimeter.

While our data on the point will not bear strict statistical evaluation, others have observed this tendency for patients with rheumatoid arthritis to evidence

a subnormal adrenocortical response to a given stimulus.[4] Whether functional insufficiency of the adrenal cortex is secondary to chronic debility or a primary factor in predisposing to the disease is at present unknown.

Other Leukocytes.—Total leukocyte count and differential count for the group of normal controls before and four hours after combined therapy failed to indicate any consistent or significant change with respect to any elements except eosinophils.

Blood Dextrose.—Administration of combined therapy twice per day for two days did not alter the dextrose tolerance of two diabetic patients tested.

Urinary Uric Acid Excretion.—Measurements of urinary uric acid after combined therapy were belatedly discovered to be valueless because of interference by the large quantities of ascorbic acid present.

Other Urinary Constituents.—Two normal young men were placed on fixed diets of ordinary composition, and urine was collected for 24 hours prior to, and for periods of four hours and 24 hours following, the injection of desoxycorticosterone acetate and ascorbic acid in combination. No change of significance was noted in the values for urinary sodium, nitrogen, corticoids or 17-ketosteroids as a result of the combined injection.

COMMENT

It is manifestly difficult to obtain statistically satisfactory controls for trials of therapy in rheumatoid arthritis. This undoubtedly has contributed to the phenomenon whereby almost any form of treatment produces reported improvement in about half the patients.

The improvement rate, nine of 16, in our adequately tested patients, does not significantly exceed this proportion. However, it is possible that greater significance should be accorded improvement in chronic cases previously refractory to nonspecific treatment.

It is inevitable now that proposed therapies for rheumatoid arthritis will be compared with cortisone in their effectiveness. Certainly the response to combined therapy in no way compares with that which follows the use of ACTH or cortisone, nor have we produced any evidence in metabolic studies in man or experimental animals[5] to support the view that combined administration of desoxycorticosterone acetate and ascorbic acid results in an effective increase in glucocorticoids. Discharge of glucocorticoids incidental to the minor alarming stimulus of intravenous injections per se would not ordinarily approach therapeutic levels. We do not have sufficient data to evaluate properly the effect of ascorbic acid alone, but in several cases in which it was so used no improvement resulted.

Although at the moment there is no logical explanation for a possible mode of action, it is perhaps too soon to deny the possibility that the observed clinical effects following the use of desoxycorticosterone acetate and ascorbic acid may be partly explained on the basis of a pharmacologic effect on joint tissues. No

4. Proceedings of First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950.

5. Schaffenburg, C.; McKendry, J. B. R., and McCullagh, E. P.: Combined Administration of Desoxycorticosterone Acetate and Ascorbic Acid: II. Experimental Observations, A. M. A. Arch. Int. Med., this issue, p. 190.

satisfactory explanation exists for the action of gold, and, partly because of this, there has been a delay of almost two decades in the general acceptance of gold as a useful agent in the management of rheumatoid arthritis.

Combined therapy with desoxycorticosterone acetate and ascorbic acid should certainly not be used indiscriminately without regard to the dangers of salt and water retention from overdosage of the desoxycorticosterone. We have encountered slight edema readily amenable to salt restriction in a few patients, but none of our patients receiving prolonged therapy with this substance have shown significant change in blood pressure or other evidence of chronic intoxication. However, until a definitive cure is available, rheumatoid arthritis will continue to require long term management. In the light of Selye's observations of the deleterious effects of mineralocorticoids on experimentally produced diseases of adaptation, the prolonged use of desoxycorticosterone acetate should be carefully supervised and on a limited scale. This is particularly important since arthritis has been produced with this hormone in the rat [6] and guinea pig [7] and has been reported in men after its clinical use.[8]

There are two situations in which short term combined therapy may be worthy of further trial: One is in conjunction with the institution of gold treatment, where it might be hoped to control symptoms until the more delayed action of gold salts becomes effective; the other is in cases in which physical therapy is hampered by severe pain which limits its effective application.

SUMMARY

Combined treatment with desoxycorticosterone acetate and ascorbic acid was used in 23 patients with rheumatoid arthritis. Of 16 patients who received more than two treatments, nine reported definitive subjective or objective improvement within a few days. An attempt is made to analyze the factors which may have contributed to the response. After liberally discounting the probable influence of weather, suggestion and other therapies, sufficient evidence for a pharmacologic action remains in some cases to warrant further restricted trials of the method. The unlikely possibility of cortisone-like activity was ruled out by eosinophil counts before and after combined therapy in patients and normal volunteers. Furthermore, there was no effect from combined therapy on dextrose tolerance, urinary nitrogen, electrolytes, 17-ketosteroids or corticoids.

233 Metcalfe Street, Ottawa, Ont., Canada (Dr. McKendry).

The desoxycorticosterone acetate used in these studies was supplied by Dr. Edward Henderson, of the Schering Corporation, Bloomfield, N. J.

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6. Selye, H.; Sylvester, O.; Hall, C. E., and Leblond, C. P.: Hormonal Production of Arthritis, J. A. M. A. **124**:201 (Jan. 22) 1944. Pirozynski, W., and Akert, K.: Polyarthritis und Nebennierenrindenhormone, Schweiz. med. Wchnschr. **30**:745 (Aug. 20) 1949. Pemberton, R.; Eiman, J.; Patterson, F. M., and Stackhous, E. A.: Attempts at Experimental Production of Arthritis, J. Lab. & Clin. Med. **32**:1121 (Sept.) 1947.

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8. de Gennes, L.; Mahoudeau, D., and Bricaire, H.: Manifestations rhumatismales provoquées par les injections ou les implants d'acétate de désoxycorticostérone, Bull. et mém. Soc. méd. d. hôp. de Paris **63**:532 (June) 1947. Laroche, G.: Sur 2 cas de rhumatismes subaigu des genoux chez des addisoniens traités par l'acétate de désoxycorticostérone, ibid. **63**:616 (June) 1947.

COMBINED ADMINISTRATION OF DESOXYCORTICOSTERONE ACETATE AND ASCORBIC ACID

II. Experimental Observations

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IN NOVEMBER 1949, Lewin and Wassén [1] reported beneficial effects from the use of combined desoxycorticosterone acetate and ascorbic acid in treatment of rheumatoid arthritis. The numerous contradictory reports since that time have been reviewed in the preceding article,[2] in which we attempted to evaluate this treatment in rheumatoid arthritis.

The present communication concerns a study in experimental animals of the effects of concurrent administration of desoxycorticosterone acetate and ascorbic acid. It is known that chronic overdosage with this hormone in the rat leads to development of typical lesions in the heart, kidneys and arteries, with elevation of arterial blood pressure,[3] and under certain experimental conditions to development of arthritis.[4] Recently, Selye [5] has reported the aggravation of formaldehyde-induced "arthritis" in rats by use of desoxycorticosterone acetate and its prevention or cure by administration of cortisone or pituitary adrenocorticotropic hormone

From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

1. Lewin, E., and Wassén, E.: Effect of Combined Injections of Deoxycortone Acetate and Ascorbic Acid on Rheumatoid Arthritis, Lancet **2**:993 (Nov. 26) 1949.

2. McKendry, J. B. R.; Schaffenburg, C., and McCullagh, E. P.: Combined Administration of Desoxycorticosterone Acetate and Ascorbic Acid: I. Clinical Results in Rheumatoid Arthritis and Laboratory Studies, A. M. A. Arch. Int. Med., this issue, p. 190.

3. (*a*) Selye, H.: General Adaptation Syndrome and the Diseases of Adaptation, J. Clin. Endocrinol. **6**:117 (Feb.) 1946. (*b*) Selye, H., and Hall, C. E.: Pathologic Changes Induced in Various Species by Overdosage with Desoxycorticosterone, Arch. Path. **36**:19 (July) 1943; (*c*) Production of Nephrosclerosis and Cardiac Hypertrophy in Rat by Desoxycorticosterone Acetate Overdosage, Am. Heart J. **27**:338 (March) 1944. (*d*) Selye, H.; Hall, C. E., and Rowley, E. M.: Malignant Hypertension Produced by Treatment with Desoxycorticosterone Acetate and Sodium Chloride, Canad. M. A. J. **49**:88 (Aug.) 1943. (*e*) Masson, G. M. C.; Corcoran, A. C., and Page, I. H.: Experimental Vascular Diseases Due to Desoxycorticosterone Acetate and Anterior Pituitary Extract, J. Lab. & Clin. Med. **34**:1416 (Oct.) 1949.

4 (*a*) Selye, H.; Sylvester, O.; Hall, C. E., and Leblond, C. P.: Hormonal Production of Arthritis, J. A. M. A. **124**:201 (Jan. 22) 1944. (*b*) Pirozynski, W., and Akert, K.: Polyarthritis und Nebennierenrindenhormone, Schweiz. med. Wchnschr. **30**:745 (Aug. 20) 1949.

5. Selye, H.: Further Studies Concerning Participation of Adrenal Cortex in Pathogenesis of Arthritis, Brit. M. J. **2**:1129 (Nov. 19) 1949.

(ACTH). Brownlee,[6] using Selye's technic, reported beneficial effects on this form of arthritis from combined administration of desoxycorticosterone acetate and ascorbic acid. To investigate whether ascorbic acid when combined with this hormone exhibits glucocorticoid properties or protects against overdosage effects of the desoxycorticosterone, several experiments were carried out.

EXPERIMENTS AND RESULTS

Cold Test.—Unlike the rat, the mouse receives slight protection against cold exposure [7] from large doses of desoxycorticosterone acetate. However, the effectiveness of the substance in this respect is much less than that of glucocorticoids.

Method: Twenty-eight male white mice, weighing from 20 to 25 Gm. and adrenalectomized on the day of the experiment, were used. Half of them received intraperitoneally 2 mg. of desoxycorticosterone acetate dissolved in 0.1 cc. of sesame oil, and the other half the same amount of the hormone plus 10 mg. of sodium ascorbate (p_H 7.0) in 0.1 cc. of solution, by the same route. The animals were then isolated in cages containing two mice each, placed in the cold room at a temperature of 10.0 C. ± 1 degree (C.), and the mortality rate was recorded every hour throughout the day.

Results: There was no difference in the mean survival time between the two groups, and all animals were dead at the end of 10 hours.

Formaldehyde-Induced "Arthritis" in the Adrenalectomized Rat.—Eight female Sprague-Dawley rats, weighing about 150 Gm. each, were used. They were adrenalectomized and divided into two groups of four rats each. Both groups received 1 per cent sodium chloride solution as drinking fluid. Group I was given daily subcutaneous injections of 5 mg. of desoxycorticosterone acetate; group II received daily, in addition to the desoxycorticosterone, 50 mg. of ascorbic acid intraperitoneally. On the third day after adrenalectomy, all rats were given 0.1 cc. of 4 per cent formaldehyde solution [5] underneath the plantar fascia of the right hindpaw and the treatment with desoxycorticosterone acetate and ascorbic acid was continued as before. Three days after the injection of formaldehyde solution there was no difference in the degree of swelling between the two groups.

Thinking that perhaps the presence of the adrenal glands was critical in the effects of the combined therapy with desoxycorticosterone and ascorbic acid, we then grafted into the left groin of all animals demedullated adrenal glands from male donors. On the following day 0.1 cc. of 4 per cent formaldehyde solution was again injected into the right hindpaw of all animals, and treatment with desoxycorticosterone acetate and ascorbic acid was continued. Seven days later the experiment was terminated. Although the paw into which the injection was made was somewhat less swollen in the animals receiving ascorbic acid than in those receiving desoxycorticosterone alone, the difference was in no way striking. Microscopically, there was slight synovial reaction in both groups. Weights of thymus, heart and kidneys did not show any difference between the two groups.

Examination of the adrenal-transplanted areas showed cortical tissue with good staining properties, although with some areas of necrosis and slight peripheral connective tissue reaction.

Egg White Reaction, Formaldehyde "Arthritis" and Desoxycorticosterone Overdosage Phenomena in Unilaterally Nephrectomized Rats.—Methods: Thirty-eight female Sprague-Dawley rats, weighing about 150 Gm. each, were employed; all of them were unilaterally nephrectomized and given 1 per cent sodium chloride solution to drink. They were then divided into four groups of eight rats each and a last one of six, which were left as untreated controls; groups I, II and III had subcutaneous implantation of two 35 mg. pellets of desoxycorticosterone acetate at the time nephrectomy was performed and through the same incision; group IV was left untreated until later in the experiment, when ACTH therapy was instituted; groups II and III received 50 mg. of ascorbic acid intraperitoneally, group II from the beginning of the experiment and

6. Brownlee, G.: Effect of Deoxycortone and Ascorbic Acid on Formaldehyde-Induced Arthritis in Normal and Adrenalectomized Rats, Lancet **1**:157 (Jan. 28) 1950.

7. Dorfman, R. I.; Shipley, R. A.; Schiller, S., and Horwitt, B. N.: Studies on "Cold Test" as Method for Assay of Adrenal Cortical Steroids, Endocrinology **38**:165 (March) 1946.

group III after formaldehyde "arthritis" was produced. Blood pressure was taken in groups I (desoxycorticosterone acetate alone) and II (desoxycorticosterone acetate and ascorbic acid) at regular intervals by two different plethysmographic methods.[8] Twenty-one days after initiation of the experiment animals in groups I (desoxycorticosterone), II (desoxycorticosterone and ascorbic acid) and V (controls) were given 0.2 cc. of fresh egg white intraperitoneally. On the thirty-first day of the experiment four rats in each of groups I (desoxycorticosterone acetate), II (desoxycorticosterone acetate plus ascorbic acid), IV (ACTH) and V (controls) were put in metabolism cages and their urine output was measured. Four days later, when urine excretion was stabilized, animals in group IV were given 5 mg. of ACTH daily, divided into four equal doses every four hours, and one week later, animals in all groups were given 0.1 cc. of 4 per cent formaldehyde solution into the right hindpaw. From then on measurements of the paw into which the injection was made and the contralateral paw, just below the ankle joint, were taken with a micrometer at regular intervals and values expressed as differences between the two measurements. Administration of ascorbic acid, 50 mg. daily intraperitoneally, was then commenced in group III, which up to that time, with the exception of the implanted desoxycorticosterone acetate, had been left untreated. The experiment was terminated two months after implantation of pellets; kidney, thymus, adrenal glands, heart and injected paws were removed, fixed in 4 per cent formaldehyde solution, weighed and sectioned.

Results: No difference was noted in the egg white edema of the two groups, that receiving desoxycorticosterone alone and that receiving the hormone plus ascorbic acid.

The blood pressure was elevated in both groups studied, with no significant difference between the two at different periods. Averages, in millimeters of mercury, were on the thirtieth day of the experiment 160 for group I (desoxycorticosterone acetate) and 157 for group II (desoxycorticosterone acetate plus ascorbic acid).

Desoxycorticosterone caused its well known diuretic effect[9] (average 65 cc. per rat per day from the thirty-first to the forty-second days of the experiment). Urine output was about 5 to 10 cc. lower throughout this period for the group receiving ascorbic acid. Both groups showed a slight decrease in urine output after administration of formaldehyde solution. ACTH exerted no diuretic effect as compared with the controls.

Contrary to expectations, the most noticeable joint swelling was observed in the groups receiving ascorbic acid, especially in the group given injections from the beginning of the experiment; groups I (desoxycorticosterone acetate) and IV (ACTH) showed the lowest values, which were not different from those of the controls. In the control group one animal which displayed suppurative arthritis had the highest values of all and was excluded from the average. Histologically, there were considerable inflammation and necrosis in the soft tissues surrounding the joints, especially at the site of injection of formaldehyde solution; these lesions were not taken into account in evaluating "arthritis," attention being concentrated exclusively on the synovial and cartilaginous changes. When thus considered, desoxycorticosterone acetate did not seem to predispose to formaldehyde "arthritis," its incidence being no higher than with ascorbic acid or ACTH administration.

Renal and Cardiac Lesions: Desoxycorticosterone acetate caused "nephrosclerosis-like" lesions in the kidney, with severe hyalinization of arteries and glomeruli. These lesions were not modified by the administration of ascorbic acid. The kidneys of animals receiving ACTH were normal. There were slight myocardial lesions in all animals receiving desoxycorticosterone acetate; use of ascorbic acid did not modify these lesions.

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8. Kempf, G. F., and Page, I. H.: Production of Experimental Hypertension and Indirect Determination of Systolic Arterial Pressure in Rats, J. Lab. & Clin. Med. **27**:1192 (June) 1942. Olmsted, F., and Glasser, O.: Graphic Measurement of Arterial Pressure in Intact Rat, Federation Proc. **8**:121 (March) 1949.

9. Masson and others.[3e] Ragan, C., and others: Syndrome of Polydipsia and Polyuria Induced in Normal Animals by Desoxycorticosterone Acetate, Am. J. Physiol. **131**:73 (Nov.) 1940. Mulinos, M. G.; Spingarn, C. L., and Lojkin, M. E.: Diabetes Insipidus-like Condition Produced by Small Doses of Desoxycorticosterone Acetate in Dogs, ibid. **135**:102 (Dec.) 1941. Winter, C. A., and Ingram, W. R.: Observations on Polyuria Produced by Desoxycorticosterone Acetate, ibid. **139**:710 (Sept.) 1943.

COMMENT

The remarkable improvement that follows cortisone and ACTH administration in rheumatic conditions is now well established.[10] Experimentally, Selye has also obtained striking results following injection of these hormones in rats with formaldehyde "arthritis."[5] Following the report of Lewin and Wassén[1] on the effects on arthritis of combined therapy with ascorbic acid and desoxycorticosterone acetate, Brownlee[6] described experiments in rats in which he observed beneficial effects from using this combination on formaldehyde-induced "arthritis."

Our results are at complete variance with those of Brownlee. The combination of desoxycorticosterone acetate with ascorbic acid did not ameliorate formaldehyde "arthritis," and it actually seemed to aggravate the condition. We have no explanation for this discrepancy other than the possible one of differences in dose, since Brownlee used 1 mg. of desoxycorticosterone acetate to 20 mg. of ascorbic acid injected daily. Our results differ also from those of Selye in that we were unable to produce a true arthritis with administration of the hormone alone in the uninephrectomized rat. Other than a few control and desoxycorticosterone-treated animals in which there was a slight synovial reaction, the lesions were localized to the site of injection of formaldehyde solution.

In view of the limited number of animals and the uncertainty regarding the function of the transplanted adrenal glands in the adrenalectomized group, the only inference which could be drawn from this experiment is in regard to the increased susceptibility of the adrenalectomized rat to desoxycorticosterone acetate.[4a] Although there was no difference in the response of the two groups treated with the hormone alone and in combination with ascorbic acid, the removal of the adrenal glands seemed to increase the arthritis-producing properties of desoxycorticosterone, as indicated by histological examination.

The possibility that the addition of ascorbic acid caused the substance to exert a cortisone-like activity was ruled out after the following considerations: (1) incubation of desoxycorticosterone with adrenal tissue yields 17-hydroxycorticosterone and not 11-dehydro-17-hydroxycorticosterone (cortisone)[11]; (2) assuming a reaction in which desoxycorticosterone was transformed into cortisone milligram for milligram, the dose (5 mg.) used clinically[1] would be therapeutically ineffective; (3) glucocorticoids, such as cortisone, have greater cold-protective properties than desoxycorticosterone[7] and the combined therapy, desoxycorticosterone acetate plus ascorbic acid, proved to offer no greater protection against cold than the desoxycorticosterone alone; (4) Dr. Lena Lewis, in our laboratories, using both the smear and counting chamber technics, found no consistent change in the blood eosinophils of the adrenalectomized mouse after administration of these two substances[12]; it is known that a drop in the circu-

10. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions, Arch. Int. Med. **85**:545 (April) 1950. Freyberg, R. H.: Effects of Cortisone and ACTH in Rheumatoid Arthritis, Bull. New York Acad. Med. **26**:206 (April) 1950.

11. Savard, K.; Lewis, L. A., and Green, A. A.: Effect of Adrenal Mince and Cell-Free Filtrate on Desoxycorticosterone, read before the Thirty-Fourth Annual Meeting of the American Societies for Experimental Biology, Atlantic City, N. J., March, 1950.

12. Lewis, L. A.: Personal communication to the authors.

lating eosinophils of the adrenalectomized mouse follows the administration of glucocorticoids [13] and that desoxycorticosterone has a negligible effect; (5) following the intraperitoneal injection of egg white in the rat, an anaphylactoid reaction develops [14] which is known to be inhibited by an alarm reaction [15] or by administration of cortisone or ACTH.[16] The combination of desoxycorticosterone acetate and ascorbic acid exerted no inhibitory effect on this reaction in our nonadrenalectomized animals.

It is now well established that after long-continued administration of desoxycorticosterone lesions result in the kidney, blood vessels and heart, with increase in blood pressure [3] and a diuresis which resembles that of diabetes insipidus.[9] None of these manifestations of desoxycorticosterone overdosage was significantly altered by the concurrent administration of ascorbic acid.

SUMMARY AND CONCLUSIONS

The effects of combined administration of desoxycorticosterone acetate and ascorbic acid to mice and rats were studied by means of the "cold test," egg white reaction and formaldehyde-induced "arthritis." It is concluded that, under the conditions of these experiments and in the doses employed, the combined administration of desoxycorticosterone acetate and ascorbic acid exerts no cortisone-like activity. Furthermore, ascorbic acid fails to modify the organic lesions resulting from overdosage of desoxycorticosterone.

ADDENDUM

Since this article was submitted for publication Coutu and Selye [17] have published their results on the use of the combination of desoxycorticosterone acetate and ascorbic acid in the experimental arthritis that follows the administration of formaldehyde solution or mustard U. S. P. in the rat. In agreement with our own observations these authors found the combination ineffective.

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Dr. Edward Henderson, of the Schering Corporation, Bloomfield, N. J., supplied the desoxycorticosterone acetate used in these studies.

Dr. John B. Hazard, head of the Department of Pathology, Cleveland Clinic, aided in the microscopic diagnosis.

13. Speirs, R. S., and Meyer, R. K.: Effects of Stress, Adrenal and Adrenocorticotropic Hormones on Circulating Eosinophils of Mice, Endocrinology **45**:403 (Oct.) 1949.

14 Selye, H.: Studies on Adaptation, Endocrinology **21**:169 (March) 1937. Leger, J.; Masson, G. M. C., and Prado, J. L.: Hypersensitivity to Egg White in Rat, Proc. Soc. Exper. Biol. & Med. **64**:366 (March) 1947.

15. Leger, J., and Masson, G. M. C.: Studies on Eggwhite Sensitivity in Rat: Influence of Endocrine Glands, Ann. Allergy **6**:131 (March-April) 1948.

16. Selye, H.: Effect of ACTH and Cortisone upon an "Anaphylactoid Reaction," Canad. M. A. J. **61**:553 (Dec.) 1949.

17. Coutu, L. L., and Selye, H.: Verification sur l'arthrite expérimentale de la valeur thérapeutique de l'acétate de désoxycorticostérone (DCA) combiné à l'acide ascorbique, Rev. canad. de biol. **9**:258 (Aug.) 1950.

Q FEVER IN CALIFORNIA

III. Aureomycin in the Therapy of Q Fever

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AFTER THE observations of Wong and Cox [1] that aureomycin was therapeutically effective in experimental Q fever in the guinea pig, a study of the usefulness of this drug in the treatment of human Q fever was undertaken. Encouraging results in an initial group of 15 patients have been reported.[2] Since that time a larger group of patients have been treated with aureomycin. The present report summarizes experience with this antibiotic over a period of one year in the treatment of Q fever in the 45 patients comprising these two groups.

PLAN OF STUDY

Aureomycin-Treated Patients.—In general, patients suspected of having Q fever were brought to our attention by physicians practicing in areas of the state where the disease appears to occur endemically or in epidemic form. With a few exceptions in which the cases chosen appeared as a part of localized outbreaks, the patients did not come to our attention unless they had been severely ill or had had an unexplained fever of several days' duration. In all, 45 patients in whom laboratory confirmation of the diagnosis of Q fever was obtained were treated with aureomycin.

Penicillin-Treated Patients.—In a retrospective examination of the clinical records of 200 patients with proved Q fever in Northern California in 1948 and 1949, it was found that somewhat over one half of these had received penicillin at some time during their illness. Of this number, there was complete information concerning the duration of fever and illness in only 25; data on these 25 patients are included here for comparison, but they are not to be considered as a control group in any strict sense. It seems reasonable to consider these patients as equivalent to untreated patients, since there is available no evidence that penicillin exerts a perceptible influence on the course of the illness.

From the Acute Communicable Disease Service and the Viral and Rickettsial Disease Laboratory, State of California Department of Public Health.

1. Wong, S. C., and Cox, H. R.: Action of Aureomycin Against Experimental Rickettsial and Viral Infections, Ann. New York Acad. Sc. **51**:290, 1948.

2. (*a*) Lennette, E. H.; Meiklejohn, G., and Thelen, H. M.: Treatment of Q Fever in Man with Aureomycin, Ann. New York Acad. Sc. **51**:331, 1948. (*b*) Brainerd, H.; Lennette, E. H.; Meiklejohn, G.; Bruyn, H. B., Jr., and Clark, W. H.: Symposium on Antibiotics: The Clinical Evaluation of Aureomycin, J. Clin. Investigation **28**:992, 1949.

DIAGNOSTIC CRITERIA

Clinical.—In the areas where Q fever was known to be occurring, a diagnosis was entertained on clinical grounds when there was a history of sudden onset of malaise, fever, severe frontal or occipital headache, retro-orbital pain, muscular aches, sweats and frank chills. Except in a few instances in which the disease was occurring in the form of a minor outbreak, a diagnosis of Q fever was not considered unless fever had been present for three or more days. Neither physical nor roentgenographic pulmonary findings were considered necessary to the diagnosis. A normal or slightly elevated white blood cell count was considered to be consistent with the diagnosis of Q fever.

Laboratory Diagnosis.—The clinical diagnosis of Q fever in both the aureomycin and the penicillin-treated groups was confirmed by one or more of the following procedures: complement fixation tests performed according to the method previously described,[3] rickettsial agglutination tests as described by Smadel[4] or the demonstration of rickettsemia due to Coxiella burnetii. In these instances rickettsemia was shown by the development of antibodies in the blood of guinea pigs inoculated intraperitoneally with whole blood from the patient and corroborated by direct microscopic demonstration of Rickettsia in the spleens of animals similarly inoculated.

In 17 patients from the two series, a fourfold or greater rise in complement-fixing antibody titer was demonstrated during the course of the illness. In 49 persons, complement-fixing antibody titers ranging from 1:64 to 1:4,096 were present while the patient was febrile; no further rises in titers (fourfold or greater) were demonstrated in subsequent tests on these persons. Complement fixation tests on the four remaining patients gave negative results; in three of these, however, the presence of C. burnetii agglutinins in the blood was proved. In the fourth patient, in whom neither complement-fixing nor agglutinating antibodies were demonstrated, a C. burnetii rickettsemia was shown on the seventh and eleventh days of illness.

Aureomycin Serum Levels.—Serum concentrations of aureomycin were determined by the method described elsewhere.[5]

THERAPY WITH AUREOMYCIN

Dosage and Route of Administration.—Twenty-five patients were treated by the oral route alone, 10 by the oral and intravenous routes combined, seven by the oral and intramuscular routes combined, two by the intramuscular route alone and one by the intravenous route alone (table 1).

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3. Lennette, E. H.; Clark, W. H., and Dean, B. H.: Sheep and Goats in the Epidemiology of Q Fever in Northern California, Am. J. Trop. Med. **29**:527, 1949.

4. Smadel, J. E.: Complement-Fixation and Agglutination Reactions in Rickettsial Diseases, in Rickettsial Diseases of Man, A Symposium, Washington, D. C., American Association for the Advancement of Science, 1948, p. 190.

5. Brainerd, H.; Bruyn, H. B., Jr.; Meiklejohn, G., and Scaparone, M.: Assay of Aureomycin in Body Fluids: Observations on Individuals Receiving Aureomycin, Proc. Soc. Exper. Biol. & Med. **70**:318, 1949.

The oral dosage ranged from 1 to 5 Gm. per 24 hours. The drug was administered in equal doses at four to eight hour intervals day and night during the period of treatment. The median number of days of treatment was five; the longest period of treatment was 24 days, during which 89 Gm. of the antibiotic was given.

The intravenous dosage was either 200 or 300 mg. per 24 hours, given in amounts of 100 mg. either twice daily at 12 hour intervals or three times per day at six hour intervals, the night dose being omitted. For administration, 100 mg. of the antibiotic was taken up in 10 ml. of a phosphate buffer (p_H 7.4) or in 5 to 10 ml. of a specially prepared *l*-leucine diluent; the solution was given from a syringe directly into an antecubital vein over a period of three to four minutes. The median number of days of therapy was four; the longest period of treatment was 12 days, over which 3,600 mg. was administered.

The intramuscular dosage ranged from 40 to 400 mg. per 24 hours, given usually twice daily in amounts of 20 to 200 mg. The antibiotic was prepared for

TABLE 1.—*Dosage and Route of Administration of Aureomycin in Forty-Five Patients with Q Fever*

Mg. per Day Parenterally		Gm. per Day Orally				Total Patients
Route	Amount	3.5 to 5.0	2.0 to 3.4	0.5 to 1.9	None	
.....	None	8	14	3	..	25
Intravenous	300	6	1	..	..	7
	200	3	..	..	1	4
Intramuscular	300 to 400	2	..	..	..	2
	100 to 300	1	1	..	..	2
	40 to 100	..	2	1	2	5
Total patients.....		20	18	4	3	45

administration by solution in 5 ml. of a phosphate buffer (p_H 7.4), with or without an equal volume of 2 per cent procaine hydrochloride, and given into the gluteal muscles. The median number of days of treatment was three; the maximum number of days was 18, during which 2,200 mg. was given.

Treatment by the intramuscular route was tried in the first four patients.[2a] Because of the severe pain and inflammation at the site of injection, this method of treatment was subsequently used only on severely ill patients who apparently did not respond to, or could not tolerate, oral medication. When aureomycin became available for intravenous use, this route supplanted the intramuscular.

Initially, the oral dosage of aureomycin was set empirically at 2 Gm. per 24 hours; this amount was chosen on the basis of the early experience of investigators treating other infectious diseases. As it became clear that all patients did not respond promptly on this dose schedule, and since it was observed that the drug apparently possesses little serious toxicity, a dosage of 4 Gm. per day was adopted as the routine. In an attempt to obtain high serum concentrations more rapidly, 2 to 4 Gm. was given by mouth in divided doses during the first two hours. Later, it was shown [5] that the intravenous injection of 50 mg. produced immediate serum concentrations equivalent to the peak levels obtained following administration of 1 Gm. orally, and this route was used in a number of patients to obtain initial high blood concentrations.

THERAPY WITH PENICILLIN

Dosage and Route of Administration.—Twenty-four of the 25 patients were treated with a repository type penicillin. The great majority of patients received between 300,000 and 800,000 units per day for a median number of seven days. The dosages employed are summarized in table 2.

TABLE 2.—*Dosage of Penicillin Received by Twenty-Five Patients with Q Fever*

Dosage, in Thousands of Units, per Day			
> 1,200	700 to 1,200	100 to 700	< 100
Number of Patients			
1	7	16	1

TABLE 3.—*Age Distribution of Aureomycin-Treated Group and Penicillin-Treated Group*

Age, Yr.	Aureomycin-Treated Group	Penicillin-Treated Group
0 to 9	..	..
10 to 19	2	..
20 to 29	8	2
30 to 39	7	8
40 to 49	12	7
50 to 59	6	4
60 to 69	7	2
70 to 79	1	2
80 +	2	..
All ages	45	25
Median age	44 yr.	44 yr.

TABLE 4.—*Age Distribution of 116 Q Fever Patients Treated with Penicillin and the Twenty-Five Pencillin-Treated Patients in the Present Series*

Age, Yr.	25 Penicillin-Treated Patients in Present Series	All Penicillin-Treated Patients
0 to 9	..	..
10 to 19	..	..
20 to 29	2	7
30 to 39	8	31
40 to 49	7	43
50 to 59	4	22
60 to 69	2	9
70 to 79	2	3
80 +	..	1
All ages	25	116

COMPARISON OF THE COMPOSITION OF THE AUREOMYCIN-TREATED SERIES AND THE PENICILLIN-TREATED SERIES

Age and Sex.—Forty of the 45 patients treated with aureomycin were males. The age range was 13 to 82 years, the median age being 44 years.

Twenty-three of the 25 patients treated with penicillin were males. The age range was 21 to 73 years, the median age again being 44 years. The distribution by age of the patients in the two groups is shown in table 3.

The 25 patients appearing in the penicillin-treated series were a part of a total of 116 patients treated with this antibiotic; only 25, as mentioned above, have been included here because data on the remainder were not complete. These 25 patients so chosen are, of course, not completely representative of the entire group treated. However, a study of table 4 indicates that so far as age distribution is concerned the smaller group is comparable to the larger.

Duration of Fever Prior to Therapy.—Table 5 summarizes data concerning the duration of fever prior to therapy in the two treated groups.

Prior to therapy with aureomycin, the duration of fever ranged from two to 32 days, with an average duration of 10 days and a median duration of seven days. (Because of the wide range of variability in the data, the median is probably the more valid figure.) Eighteen, or 40 per cent, of the aureomycin-treated patients had been ill five days or less prior to specific therapy; 13, or 29 per cent, had been ill 12 days or longer before treatment with aureomycin was begun.

TABLE 5.—*Number of Febrile Days in Seventy Patients Prior to Treatment with Aureomycin or Penicillin*

Days of Fever Before Therapy Was Begun	Number of Patients	
	Aureomycin Treated	Penicillin Treated
< 3	2	2
3 to 5	16	11
6 to 8	8	6
9 to 11	6	3
12 +	13	3
All patients	45	25
Median number days of fever prior to treatment	7	6
Average number days of fever prior to treatment	10	8

In the group treated with penicillin, the duration of fever prior to therapy ranged from one to 30 days, with an average duration of eight days and a median duration of six days. Thirteen, or 52 per cent, were ill for five days or less; only three, or 12 per cent, were febrile for 12 days or more before therapy was instituted.

From these data it appears that, except for the larger proportion of patients in the aureomycin-treated series in whom antibiotic therapy was not begun until the twelfth day of illness or later, the two series are not dissimilar in regard to duration of illness prior to treatment.

It may be thought that patients not treated until the twelfth day of illness or later would be nearing the end of the normal course of the illness without treatment and that any apparently beneficial effects of the antibiotic were largely coincidental to normal recovery. However, in all but two instances, patients in this category were still unusually ill when treatment was begun.

RESULTS OF THERAPY

The duration of fever (oral temperature of 99.2 F. or greater) was chosen as the single most objective criterion of the presence of clinical illness and for evaluation of the response to therapy. Although the use of such a criterion allows

simple tabular and statistical treatment of the data, there are obvious limitations to this procedure, since no consideration is given to symptomatic improvement in the presence of continuing fever or to the occurrence of a prolonged period of convalescence following return of the temperature to normal.

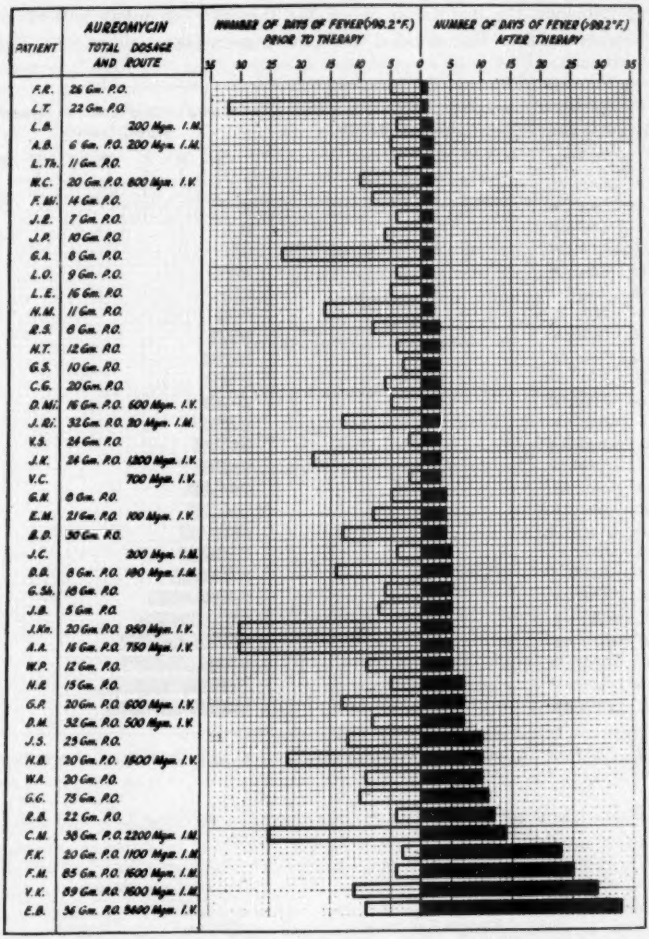
PATIENT
AUREOMYCIN TOTAL DOSAGE AND ROUTE
NUMBER OF DAYS OF FEVER(99.2°F.) PRIOR TO THERAPY
NUMBER OF DAYS OF FEVER(99.2°F.) AFTER THERAPY
35 30 25 20 15 10 5 0 5 10 15 20 25 30 35
F.R. 26 Gm. P.O.
L.T. 22 Gm. P.O.
L.B. 200 Mgm. I.M.
A.B. 6 Gm. P.O. 200 Mgm. I.M.
L.Th. 11 Gm. P.O.
W.C. 20 Gm. P.O. 800 Mgm. I.V.
F.W. 14 Gm. P.O.
J.R. 7 Gm. P.O.
J.P. 10 Gm. P.O.
G.A. 8 Gm. P.O.
L.O. 9 Gm. P.O.
L.E. 16 Gm. P.O.
N.M. 11 Gm. P.O.
R.S. 8 Gm. P.O.
N.T. 12 Gm. P.O.
G.S. 10 Gm. P.O.
C.G. 20 Gm. P.O.
D.M. 16 Gm. P.O. 600 Mgm. I.V.
J.R. 32 Gm. P.O. 20 Mgm. I.M.
V.S. 24 Gm. P.O.
J.K. 24 Gm. P.O. 1200 Mgm. I.V.
V.C. 700 Mgm. I.V.
G.K. 8 Gm. P.O.
E.M. 21 Gm. P.O. 100 Mgm. I.V.
R.B. 30 Gm. P.O.
J.C. 200 Mgm. I.M.
D.B. 8 Gm. P.O. 100 Mgm. I.M.
G.Sh. 18 Gm. P.O.
J.B. 5 Gm. P.O.
J.Kn. 20 Gm. P.O. 950 Mgm. I.V.
A.A. 16 Gm. P.O. 750 Mgm. I.V.
W.P. 12 Gm. P.O.
N.R. 15 Gm. P.O.
G.P. 20 Gm. P.O. 600 Mgm. I.V.
D.M. 32 Gm. P.O. 500 Mgm. I.V.
J.S. 23 Gm. P.O.
H.B. 20 Gm. P.O. 1800 Mgm. I.V.
W.A. 20 Gm. P.O.
G.G. 75 Gm. P.O.
R.B. 22 Gm. P.O.
C.M. 38 Gm. P.O. 2200 Mgm. I.M.
F.K. 20 Gm. P.O. 1100 Mgm. I.M.
F.M. 85 Gm. P.O. 1600 Mgm. I.M.
V.K. 69 Gm. P.O. 1600 Mgm. I.M.
E.B. 36 Gm. P.O. 3600 Mgm. I.V.

Fig. 1—Duration of fever in 45 patients prior to and after institution of treatment with aureomycin. *P.O.* indicates the oral route was used, *I.M.*, the intramuscular route, and *I.V.*, the intravenous route.

In table 6 and figure 1 data are presented which show that in the aureomycin-treated series the duration of fever after therapy was begun ranged from one to 33 days, with an average duration of six days and a median duration of three days.

In this series, after treatment with aureomycin, 13, or 29 per cent, of the patients had become afebrile (temperature of less than 99.2 F.) in less than three days; 22, or 49 per cent, had become afebrile in three days, and 32, or 71 per cent, had become afebrile in five days or less.

A total of 13 patients in this group did not become afebrile until more than five days following the institution of specific therapy. In many patients in this category, however, there was decided subjective improvement within 48 to 72 hours,

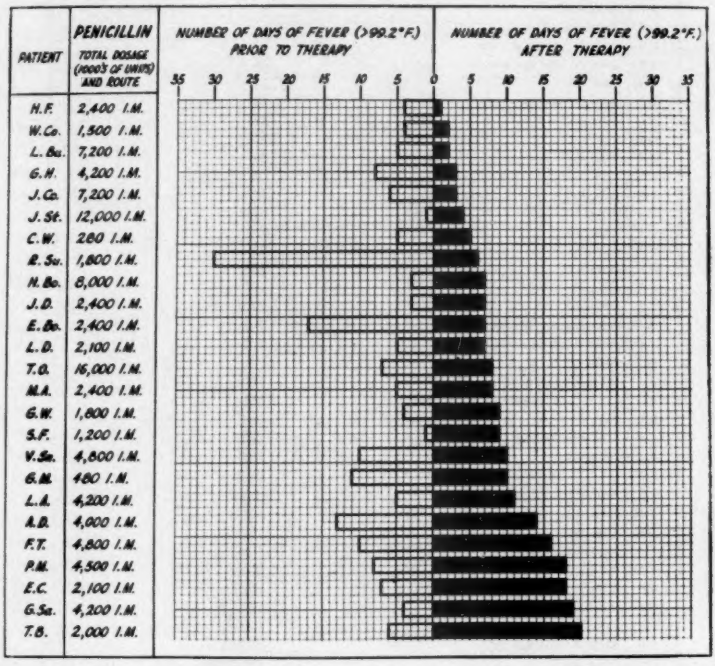

Fig. 2.—Duration of fever in 25 patients prior to and after institution of treatment with penicillin.

TABLE 6.—*Number of Febrile Days in Seventy Patients After Treatment with Aureomycin or Penicillin*

Days of Fever After Therapy Was Begun	Number of Patients	
	Aureomycin Treated	Penicillin Treated
< 3	13	3
3 to 5	19	4
6 to 8	3	7
9 to 11	4	5
12 +	6	6
All patients	45	25
Median days of fever after treatment was begun	8	8
Average days of fever after treatment was begun	6	9

often accompanying a relatively sharp drop in body temperature, followed by several days of low grade fever before the temperature returned to normal. This slower, less dramatic apparent response to therapy characterized the course of several of the patients who are shown in figure 1 to have had a febrile period of more than three days following the institution of treatment with aureomycin. One such clinical course is illustrated in figure 3.

This patient, W. A., noted slight malaise and generalized aching for 24 hours before the occurrence of a severe chill and elevation in temperature to 105.4 F. The first week of illness was marked by repeated chills, high fever, headache and generalized body aches. He was hospitalized on the eighth day of illness without a definite clinical diagnosis. There were no significant physical findings. Typhoid, paratyphoid and Brucella agglutinins were not present in significant titers. Smears for malarial parasites and repeated blood cultures showed no

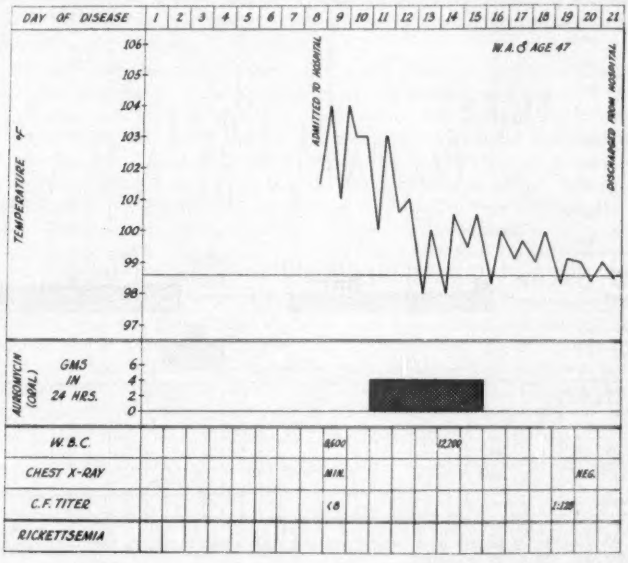

Fig. 3.—Course of illness in a patient treated with aureomycin, in which the apparent response to therapy was partial.

organisms. The white blood cell count was 8,600, with 65 per cent neutrophils. A chest roentgenogram was interpreted as "suggestive of atypical pneumonia." A complement fixation test for Q fever performed on a specimen taken on the eighth day of illness gave negative results; on the nineteenth day of illness the titer had risen to 1 : 128.

On the tenth day of illness, a tentative diagnosis of Q fever was made and treatment with aureomycin was instituted. Four grams was given by mouth daily for five days. On the second day of therapy considerable subjective improvement was noted in the patient's condition.

By the third day of treatment the patient felt quite well, but an elevation in temperature ranging up to 101.5 F. persisted for six more days. On the third day of treatment it was first observed that the patient's liver was palpable 4 cm. below the right costal margin and was slightly tender.

The remainder of the patient's stay in the hospital was uneventful; on the twentieth day of illness physical examination revealed no abnormality; a chest roentgenogram was interpreted as normal. The patient was discharged from the hospital on the twenty-first day of illness and remained well thereafter.

From table 6 and figure 2 it may be seen that in the penicillin-treated series the duration of fever after the institution of therapy ranged from one to 20 days, with an average of nine days and a median of eight days. Three, or 12 per cent, of the patients in this series became afebrile in less than three days after treatment with penicillin was begun; seven, or 28 per cent, became afebrile in five days or less, and the remainder, or 60 per cent, had not become afebrile in five days or less.[6]

In general, there was no marked subjective improvement in the penicillin-treated patients following the beginning of therapy, nor did the return of the body temperature to normal follow the pattern illustrated in figure 3, which was characteristic of several patients treated with aureomycin.

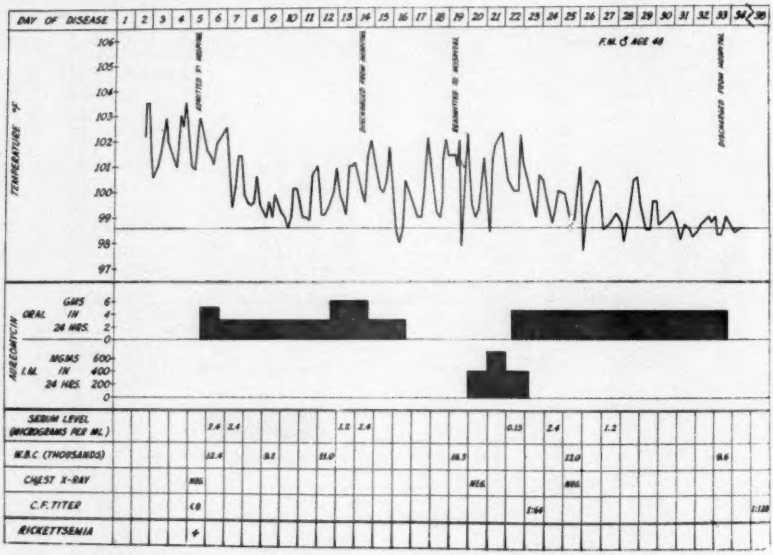

Fig. 4.—Course of illness in a patient treated with aureomycin, in which apparent response to therapy was absent or minimal.

In both the aureomycin-treated and the penicillin-treated patients, as shown in figures 1 and 2, it seems probable that in certain of the patients in whom fever disappeared promptly after the institution of therapy (for example, F. R. and L. T. in figure 1, H. F. in figure 2) the antibiotic was not wholly responsible. At the other extreme of the aureomycin-treated series, there were four or five patients in whom response to treatment with aureomycin was not apparent.

Certain clinical and laboratory data for one of these patients are presented in figure 4.

6. If the return of temperature to normal limits within five days or less is taken as the point of dichotomy in setting up a fourfold table for these series, the chi-square is 12.1. In the usual interpretation of chi-square, this value indicates that in considerably less than one trial in 100 could such a deviation between the two series be expected due to chance alone.

This patient, F. M., a manager of a sheep ranch, had a sudden onset of fever (elevation in temperature to 103.8 F.) but without chills. He complained of chilly sensations, soreness in the neck and back, moderately severe but persistent headache and retro-orbital pain. There was a slight nonproductive cough, accompanied with mild pain in the chest. A physical examination five days after onset was stated to reveal no abnormal findings; a chest roentgenogram at the same time was reported as revealing "slightly increased bronchovascular markings." He was admitted to the hospital with a diagnosis of Q fever, and treatment was begun with 4.0 Gm. of aureomycin orally per day.

A complement fixation test performed on the fifth day of illness gave negative results, but C. burnetii was recovered from the blood at this time. On the twenty-third day of illness the complement-fixing antibody titer was 1 : 64, and on the thirty-eighth day after onset it was 1 : 128.

After the institution of treatment with aureomycin, there was some subjective improvement within two days, and the patient's temperature began to fall slowly toward normal. However, his temperature ranged between 99.2 and 101 F. until the fourteenth day of illness, when he left the hospital at his own request. Aureomycin was administered orally for two days after he had left the hospital.

Readmitted to the hospital on the nineteenth day of illness, with an elevation in temperature to 102 F. and complaints similar to those during his first hospitalization, the patient showed no significant physical findings. The white blood cell count, which had previously been in the neighborhood of 10,000, was 16,300, with 82 per cent polymorphonuclear cells, at his second hospital admission. Cold agglutinins, typhoid, paratyphoid and Brucella agglutinins were not present in significant titer. A chest roentgenogram was interpreted as normal. Aureomycin was given intramuscularly, 400 mg. the first day, 700 mg. the second, 400 mg. the third and 100 mg. the fourth. At this time, oral administration of the antibiotic was resumed in the amount of 4.5 Gm. daily. The remainder of his hospital course was uneventful, his temperature falling gradually but irregularly to normal on the thirtieth day of illness.

Determinations for the serum levels of the antibiotic were made on six occasions in the period during which the drug was given orally. Blood for each determination was obtained just prior to the administration of a dose of aureomycin, i. e., about three and one half to four hours had elapsed since a dose had been received. In four instances the serum concentration of aureomycin was 2.4 micrograms per milliliter; in two instances the serum level was 1.2 micrograms per milliliter. A single serum level determination made on the third day of therapy with the drug given intramuscularly gave a reading of only 0.15 microgram per milliliter of serum.

The course followed by a second patient who apparently did not respond to specific therapy is shown in figure 5.

This patient, V. K., owner of a sheep ranch, became ill suddenly with severe headache, malaise, frank chills and an elevation in temperature to 103 to 105 F. She was mildly nauseated but exhibited no symptoms referable to the respiratory tract. No findings of significance were encountered on physical examination on the eighth day of illness. She was admitted to the hospital with a tentative diagnosis of Q fever, and therapy with aureomycin was begun on the ninth day of illness.

On her entry to the hospital, a complement fixation test for C. burnetii gave negative results, but the titer on the twenty-fifth day of illness was 1 : 512. Rickettsemia was demonstrated on the ninth day of illness, before therapy was begun. A white blood cell count at this time was 7,300, with 73 per cent polymorphonuclear cells. Typhoid, paratyphoid and Brucella agglutination tests gave negative reactions throughout the illness.

The patient was given a large initial dose of aureomycin by mouth (8 Gm. during the first 24 hours) and 5 Gm. daily thereafter for eight days. During this time considerable difficulty was experienced with nausea and frequent vomiting following administration of the drug. Chills and high fever persisted for four days after institution of therapy; although the patient experienced no further chills after this time, the fever persisted and there was no subjective improvement.

Because of the gastrointestinal difficulties encountered with the oral administration of the antibiotic, it was then given intramuscularly, at a rate of 400 mg. per day, for four days. This

process proved extremely painful; there was no apparent beneficial effect, and intramuscular therapy was supplanted by oral administration on the twenty-fourth day of illness. Although this form of therapy was continued for five more days, no definite improvement was noted in the patient's condition. She appeared, however, to be less seriously ill than when admitted and was allowed to go home on the thirty-second day of illness. She continued to show an elevated temperature for one week after returning home and complained of weakness and fatigability for several months.

Serum level determinations for aureomycin were made on four occasions during oral therapy. As shown in figure 5, the values obtained, between 0.64 and 1.2 micrograms per milliliter, were similar to those obtained in patients apparently responding to specific treatment. A single determination made during the course of intramuscular therapy gave a serum concentration of less than 0.15 microgram per milliliter. In view of this finding, the period of intramuscular administration can hardly be considered as one of adequate therapy.

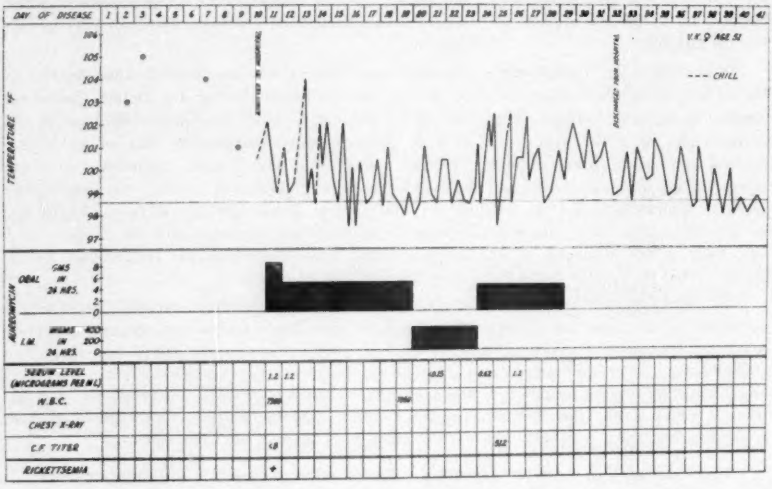

Fig. 5.—Course of illness in a patient treated with aureomycin, in which apparent response to therapy was not observed.

TOXICITY

All patients treated with aureomycin were observed carefully for evidence of toxicity due to the antibiotic. Gastrointestinal symptoms comprised the most frequent and troublesome toxic manifestations noted. Almost 60 per cent of the patients given the drug orally complained of nausea, ranging from mild to severe. None of the lots of drugs used appeared to be devoid of this property.

In the smaller series of patients described in an earlier paper,[2a] one patient complained of soreness and pruritus of the scrotum and of soreness of the oral mucosa. A second person also complained of soreness of the scrotum, and in addition a few pruritic papular lesions developed over the shoulders. None of these manifestations was noted in any other of the patients receiving aureomycin.

There was no evidence in any patient treated with aureomycin of disturbance of the central or peripheral nervous system.

A urinalysis and complete blood count were performed before initiation of therapy and repeated at intervals while therapy was in progress. In no instance was there evidence of depression of either the white or the red cell series. In one instance, albumin and red cell casts appeared in the urine on the fifth day of therapy; treatment was continued, and the urine became normal on the seventh day.

No serious difficulties were encountered in the use of the antibiotic intravenously, even though as much as 300 mg. of the drug was given at one time. On two occasions the drug was given accidentally into the tissues surrounding the vein; pain occurred at the site of injection for a few hours, but subsequent reaction was limited to redness and induration for a few days.

RICKETTSEMIA FOLLOWING TREATMENT WITH AUREOMYCIN

In table 7 appear the results of attempts to detect rickettsemia in patients treated with aureomycin. A total of 27 specimens from 21 persons was examined for the

TABLE 7.—*Recovery of Coxiella Burnetii from the Blood of Aureomycin-Treated Patients, Prior to and Following Therapy*

Days of Treatment	Number of Specimens Tested	Number Positive
Prior to treatment	14	8
1	3	3
2	5	4
3	1	1
4 to 9	..	..
10	1	..
11	1	..
12	..	..
13	1	1*
14 to 17	..	..
18	1	..
Total	27	17

* C. burnetii recovered eighth day after discontinuance of therapy.

presence of rickettsiae. Of 14 specimens of blood obtained from 14 patients before therapy, rickettsemia was demonstrated in eight specimens from eight patients.

Of nine specimens taken from five patients during the first three days of therapy, C. burnetii was detected in eight. Serum concentrations of aureomycin in two patients during the period of rickettsemia were as high as 9.9 micrograms per milliliter.

This indicates that rickettsiae may be recovered from the circulating blood despite the attainment of relatively high serum concentrations of aureomycin. It is also interesting to note that rickettsiae may be recovered after objective and subjective improvement has occurred in the condition of the patient. Smadel [7] made similar observations in the treatment of scrub typhus with chloramphenicol (chloromycetin®).

The presence of rickettsemia later than the third day of treatment was demonstrated in one patient eight days after treatment had been discontinued. This

7. Smadel, J. E.: Evaluation of New Drugs in the Treatment of Rickettsial Diseases, Bull. Pan-Am. San. Bureau **28**:1, 1949.

patient (J. Kn.) had been ill for about one month before treatment was begun. During this time he had had a daily elevation of temperature to 101 or 102 F. At the time treatment was started, a few rales were heard at the bases of both lungs and his liver was noted to be enlarged and slightly tender. He became afebrile on the fifth day following the beginning of treatment with aureomycin and remained so thereafter. Treatment was continued one more day; a blood specimen taken eight days later was inoculated into two guinea pigs. At the end of 30 days, both animals had developed complement-fixing antibodies against C. burnetii.

COMMENT

Evaluation of the effectiveness of aureomycin in the treatment of this disease would be considerably simpler if all patients had recovered promptly after institution of therapy, thereby demonstrating the efficacy of the drug. On the other hand, if aureomycin had not appeared to influence in any instance the course of illness, it would be reasonable to state that aureomycin in the amounts and manner used is no more effective than penicillin in the treatment of Q fever. The results observed actually lay between these two extremes.

Briefly, there appeared in this series to be three general types of response to treatment with aureomycin. First were those patients who appeared to show a favorable response to therapy. Thirty-two (71 per cent) of 45 patients treated with aureomycin became afebrile in five days or less after therapy was begun; in this group are, no doubt, included some patients who would have become afebrile in a short time without treatment. Even so, of those patients treated with penicillin, only seven of 25, or 28 per cent, became afebrile in the same period.

The second group included those persons who showed a less favorable response to treatment with aureomycin. There were in this group nine patients who did not become completely afebrile in five days or less but nevertheless showed subjective improvement and a decided drop in temperature as compared with that prior to treatment. No such effects were noted among the patients treated with penicillin.

The third group of four patients showed either minimal or no improvement during the course of treatment. The course followed by two of these patients has been described in detail above.

Thus, it appears that aureomycin in the dosage used in this series is useful in the treatment of Q fever, but it is equally apparent that the antibiotic is not invariably effective in influencing the course of illness.

The reasons for the apparent failure of therapy in the four patients mentioned above are not clear. The dosage of aureomycin received by these persons was as great as or greater than that received by others in whom a more favorable response occurred. Serum concentrations of the antibiotic in these patients were never high, except in the one patient who received the drug intravenously; however, the majority of serum levels observed in these patients were similar to the levels in patients whose apparent response was more favorable. The possibility of the existence of several strains of C. burnetii having varying sensitivities to aureomycin has not been investigated but may be a factor in determining the efficacy of the antibiotic in treatment of this disease.

Data obtained in experimental animals[1] show that C. burnetii is susceptible to the action of aureomycin. The observation that in man C. burnetii may be recovered from the circulating blood for at least three days after treatment has been instituted suggests that the dosages used in this series may not have been large enough to be effective in all infections. In view of the minor toxic effects which may be attributed to aureomycin, it appears that in the treatment of infections with C. burnetii increased dosages may be indicated. The efficacy of larger dosages by either the oral or the intravenous routes remains to be established.

SUMMARY AND CONCLUSIONS

Forty-five patients with Q fever were treated with aureomycin, and the results are compared with those in a series of 25 patients who had received penicillin.

Treatment with aureomycin appeared to effect a significant reduction in the duration of fever, and the antibiotic is considered to be useful in the treatment of this disease. In some patients, however, response to aureomycin therapy appeared to be slight or negligible; no satisfactory explanation of these therapeutic failures was established.

THE EISENMENGER COMPLEX AND ITS RELATION TO THE UNCOMPLICATED DEFECT OF THE VENTRICULAR SEPTUM

Review of Thirty-Five Autopsied Cases of Eisenmenger's Complex, Including Two New Cases

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AND
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VICTOR Eisenmenger [1] in 1897 reported the case of a cyanotic adult who at autopsy was observed to have a large ventricular septal defect. Twenty-five years later, Maude Abbott [2] brought into focus the fact that in Eisenmenger's case the aorta was overriding the defect of the septum. She separated this malformation from the simple ventricular septal defect on one hand and the tetralogy of Fallot on the other and named it "the Eisenmenger complex." In the last few years this syndrome has attracted much attention, as the diagnosis of the Eisenmenger complex was considered to be a contraindication for the performance of surgical procedures devised for the relief of cyanosis.

The Eisenmenger complex is usually presented as a cyanotic form of congenital heart disease consisting of a high defect of the ventricular septum, the aorta overriding the defect and dilatation of the pulmonary vessels, with an unobstructed pulmonary orifice. As in the tetralogy of Fallot, the hypertrophy of the right ventricle may be added as the fourth feature, and the term "tetralogy of Eisenmenger" has been used by several authors.[3]

In a previous communication [4] it was shown that no strict dividing line exists between uncomplicated larger defects of the ventricular septum and the Eisenmenger complex. It was suggested that the most important feature distinguishing the Eisenmenger complex from the ventricular septal defect is the presence of anoxemia in the former and its absence in the later syndrome.

The purpose of this communication is to present further evidence of the similarity between the large ventricular septal defect and the Eisenmenger com-

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1. Eisenmenger, V.: Die angeborenen Defecte der Kammerscheidewand des Herzens, Ztschr. f. klin. Med. **32**(supp.): 1, 1897.

2. Abbott, M. E., and Dawson, W. T.: Clinical Classification of Congenital Heart Disease, Internat. Clin. **4**:156 (Dec.) 1924.

3. (*a*) Saphir, O., and Lev, M.: The Tetralogy of Eisenmenger, Am. Heart J. **21**:31 (Jan.) 1941. (*b*) Talley, J. E., and Fowler, K.: Tetralogy of Fallot (Eisenmenger Type) with Hypoplasia of the Dextroposed Aorta, Am. J. M. Sc. **191**:618 (May) 1936.

4. Selzer, A.: Defect of the Ventricular Septum: Summary of 12 Cases and Review of the Literature, Arch. Int. Med. **84**:789 (Nov.) 1949.

plex and to discuss circulatory dynamics differentiating these syndromes. This is based on a pathological-clinical correlation of 33 cases collected from the literature [5] and two cases in adults reported here for the first time.

REPORT OF CASES

CASE 1.—A 57 year old optician entered the medical ward of Stanford University Hospitals on April 3, 1946 because of chills and fever.

He was known to have been cyanotic since birth, but he led a reasonably active life in spite of limitations. The only remarkable past illness was an attack, early in 1942, of congestive heart failure believed to be associated with myocardial infarction which was treated with rest in bed and digitalis. After recovery from this attack, the patient was completely free from symptoms.

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5. (*a*) Spitzer, A.: Über den Bauplan des normalen und missbildeten Herzens: Versuch einer phylogenetischen Theorie, Virchows Arch. f. path. Anat. **243**:81, 1923. (*b*) Ash, R.; Wolman, I. J., and Brenner, R. S.: Diagnosis of Congenital Cardiac Defects in Infancy: A Study of 32 Cases with Necropsies, Am. J. Dis. Child. **58**:8 (July) 1939. (*c*) von Rokitansky, C.: Die Defecte der Scheidewände des Herzens, Vienna, W. Braumüller, 1875. (*d*) Mahaim, I.: Présentation de trois observations anatomocliniques de malformations congénitales, Cardiologia **15**:298, 1949. (*e*) Rosedale, R. S.: Interventricular Septal Defect, Dextroposition of the Aorta, and Dilatation of Pulmonary Artery, Am. J. Path. **11**:333 (March) 1935. (*f*) Tesseraux, H.: Zur Kenntnis der Defekte der Herzkammerscheidewand, Virchows Arch. f. path. Anat. **289**:412, 1933. (*g*) Kurtz, C. M.; Sprague, H. B., and White, P. D.: Congenital Heart Disease: Interventricular Septal Defect with Associated Anomalies in a Series of 3 Cases Examined Post Mortem and a Living Patient 58 Years Old with Cyanosis and Clubbing of Fingers, Am. Heart J. **3**:77 (Oct.) 1927. (*h*) Baumgartner, E. A., and Abbott, M. E.: Interventricular Septal Defect with Dextroposition of Aorta and Dilatation of the Pulmonary Artery (Eisenmenger Complex) Terminating in Cerebral Abscess, Am. J. M. Sc. **177**:639 (May) 1929. (*i*) Dalrymple, J.: Diseased Heart in Which the Root of the Aorta Had an Opening Common to 2 Ventricles, Tr. Path. Soc. London **1**:58, 1848. (*j*) Wegmüller, T.: Grosser Ventrikelseptumdefekt: Insuffizienz, Aneurysma und Perforation der Arteria pulmonalis, Helvet. med. acta **16**:26 (Feb.) 1949. (*k*) Eppinger, E. C.; Burwell, C. S., and Farber, S.: Physiology and Pathology of a Patient with Eisenmenger's Syndrome, cited by Taussig,[17] p. 417. (*l*) Talley and Fowler.[3b] (*m*) Eisenmenger.[1] (*n*) Millman, S., and Kornblum, D.: Interventricular Septal Defect with Dextroposition of Aorta Without Stenosis of the Pulmonary Artery (Eisenmenger Complex) Complicated by Subacute Bacterial Endocarditis, J. Tech. Methods **15**:147 (March) 1936. (*o*) Lindeboom, G. A.: A Case of the "Eisenmenger Complex," Cardiologia **13**:90, 1948. (*p*) Abbott, M. E.: On the Incidence of Bacterial Inflammatory Processes in Cardio-Vascular Defects and in Malformed Semilunar Cusps, Ann. Clin. Med. **4**:189 (Sept.) 1925. (*q*) Paine, J. R., and Varco, R. L.: Experiences in the Surgical Treatment of Pulmonary Stenosis, Surgery **24**:355 (Aug.) 1948. (*r*) Schramm, H. G.: Schwere Herzmissbildungen bei älteren Individuen, Beitr. z. path. Anat. u. z. allg. Path. **82**:153 (June 29) 1929. (*s*) Stewart, H. L., and Crawford, B. L.: Congenital Heart Disease with Pulmonary Arteritis, Am. J. Path. **9**:637 (Sept.) 1933. (*t*) Shapiro, P. F.: Detorsion Defects in Congenital Cardiac Anomalies: Report of 3 Cases, with an Analysis of the Mechanism of Their Formation, Arch. Path. **9**:54 (Jan., pt. 1) 1930. (*u*) Coyon, A.: Affection congénitale du coeur: aorta et artère pulmonaire naissant du ventricule droit; dilatation de l'artère pulmonaire, Bull. Soc. anat. de Paris **72**:717, 1897. (*v*) Saphir and Lev.[3a] (*w*) Taussig, H. B., and Semans, J. H.: Severe Aortic Insufficiency in Association with Congenital Malformation of the Heart of the Eisenmenger Type, Bull. Johns Hopkins Hosp. **66**:156 (March) 1940. (*x*) Soulié, P.; Routier, D., and Bernal, P.: Communication interventriculaire avec insuffisance aortique (Diagnostic différentiel de la persistance du canal artériel), Arch. d. mal. du coeur **42**:765 (Aug.) 1949. (*y*) Laubry, C.; Routier, D., and Soulié, P.: Les souffles de la maladie de Roger, Rev. de méd., Paris **50**:439 (July) 1933. (*z*) Hurst, W. W., and Schemm, F. R.: High Ventricular Septal Defect with Slight Dextroposition of the Aorta (Eisenmenger's Type) Which Presented the Clinical Features of Patent Ductus Arteriosus, Am. Heart J. **36**:144 (July) 1948.

Early in 1945 urinary retention developed and gradually progressed, until, on Feb. 23, 1946, a perineal prostatectomy was performed. On the tenth postoperative day, following a bout of diarrhea, he had a chill, and the temperature rose to 38.5 C. (101.3 F.). During the next five weeks chills and spikes in temperature recurred at intervals of two to seven days. His left leg and thigh became swollen and tender. Later, tenderness extended to the left groin and both costovertebral angles.

On examination the patient was found to be emaciated, with definite cyanosis of mucous membranes and nail beds. The heart was not enlarged. A blowing systolic murmur was present at the apical area, and a high-pitched short systolic murmur was audible at the base of the heart. At times, a distinct early diastolic blowing murmur was heard at the pulmonary area. His left leg was swollen, and there was tenderness of the left groin and thigh. Other physical findings were noncontributory.

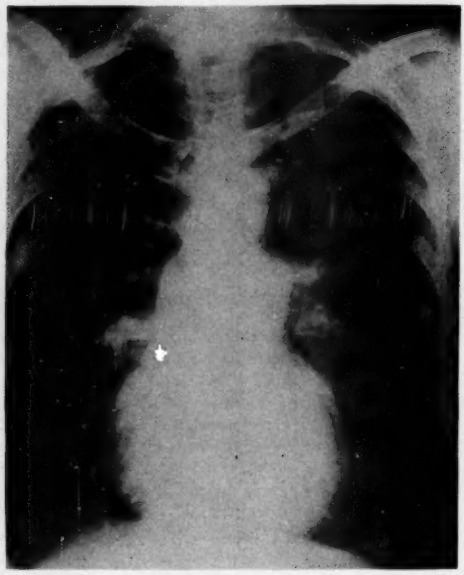

Fig. 1 (case 1).—Roentgenogram of chest showing globular cardiac enlargement, prominence of the pulmonary artery shadow and enlargement of pulmonary artery branches.

The pertinent laboratory data included repeated blood cultures, positive for Enterococcus on two occasions and for Escherichia coli on one occasion, in addition. Urine cultures grew E. coli, Aerobacter aerogenes and enterococci. During febrile periods the urinary sediment was ful of pus cells. Blood counts showed leukocytosis, the count varying from 25,000 to 35,000 cells, but the hemoglobin content and erythrocyte counts were normal.

The electrocardiogram showed delayed atrioventricular conduction time (0.24 second) and slight left axis deviation, with large Q waves in leads II and III and diphasic T waves in leads I and II.

Roentgenologic examination showed only slight cardiac enlargement, with striking prominence of the regions of the pulmonary artery and its branches and pulmonary congestion (fig. 1). The large amplitude of pulsations of the pulmonary artery segments was noted on fluoroscopy and recorded by roentgen kymography.

The patient was treated with streptomycin and showed considerable improvement; blood and urine cultures became sterile; local changes in the leg subsided, and the fever lessened.

However, on April 19 the patient suddenly began coughing up blood, became dyspneic and intensely cyanotic and died within a few minutes.

Anatomic Observations.—Summary: 1. Congenital malformation of the heart; patency of the ventricular septum and partial dextroposition of the aorta; severe hypertrophy of the right ventricle; dilatation of the right and left sides of the heart; dilatation of the pulmonary artery; severe pulmonary arteriosclerosis and arteriolosclerosis; atrophy of the central liver cells; clubbing of fingers.

2. Thrombophlebitis of the left femoral vein and iliac vein; infarction of spleen, liver and kidneys (paradoxical embolism?); perinephritic abscess; septic embolism of the right pulmonary artery; recent infarction of right lung; massive bronchial hemorrhage.

3. Generalized arteriosclerosis, with old thrombosis of the circumflex branch of the left coronary artery and healed infarction of the myocardium.

Heart and Lungs: The heart weighed 430 Gm. (body weight, 110 pounds [49.9 Kg.]). Both ventricles were dilated, and the right ventricle was hypertrophied, measuring up to 8 mm. in thickness. The right atrium was dilated. The foramen ovale was closed. The coronary sinus was dilated and opened into the auricle by a wide orifice. A large round defect involving

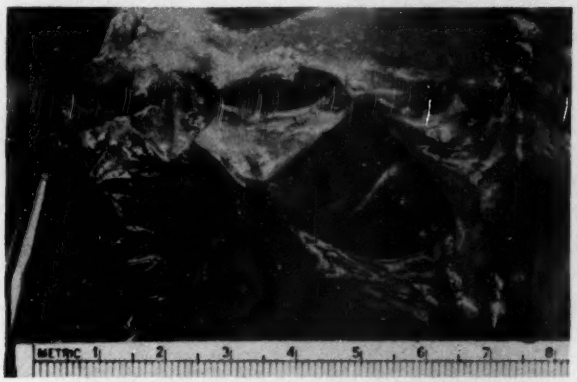

Fig. 2 (case 1).—Left ventricular aspect of membranous septum. Defect is underneath posterior aortic cusp, and aorta is overriding it. Chordae tendineae and a portion of the tricuspid leaflet are seen through defect in right ventricle.

the membranous septum and the adjacent muscular portion of the interventricular septum was noted to open into the right ventricle beneath the medial cusp of the tricuspid valve (fig. 2). The defect measured 24 mm. in width and was bordered by smooth endocardium without evidence of recent or old endocarditis. A moderate degree of dextroposition of the aorta was apparent. The aortic valve measured 67 mm., in contrast to the pulmonary valve which was dilated and measured 102 mm. The pulmonary artery was dilated and moderate coronary sclerosis was present. A recanalized thrombus was observed in the circumflex branch of the left coronary artery. An area of scarring, 5.0 by 1.5 cm., replaced the muscle of the posterior wall of the left ventricle and extended into the apex of the right ventricle. The endocardium covering the old infarct was opaque and white.

The large branches of the pulmonary artery possessed many prominent yellowish intimal plaques, and the smaller branches were dilated and yellowish and had firm walls. A roughened area about 2 cm. wide was seen in the primary branch to the lower lobe of the right lung, which histologically was highly suggestive of a septic embolism, with associated local arteritis and local aneurysmal dilatation. In this area the branches of the bronchial tree and the lung substance contained much blood. Two larger arteries to the middle lobe of the right lung, which branched off at the point of intimal roughening, were stenosed at the ostiums, and the

middle lobe of the right lung showed evidence of recent infarction. The aorta was relatively smooth and revealed only mild changes of atherosclerosis.

The local pulmonary arteritis presumably was the result of embolism from a thrombophlebitic process in the left femoral vein. Further evidence of septic embolism, probably of paradoxical nature, was observed in the spleen and kidneys.

Microscopic Changes in the Lungs: Sections taken from various lobes showed many small arteries and arterioles with pronounced fibrous thickening of the intima and prominence of the muscular media. Recanalized thrombi were clearly demonstrable in several vessels (fig. 3), and they were predominantly located in the peripheral portions of the lung. In contrast to the localized lesions due to the septic embolism, the thrombotic changes were scattered through all lobes.

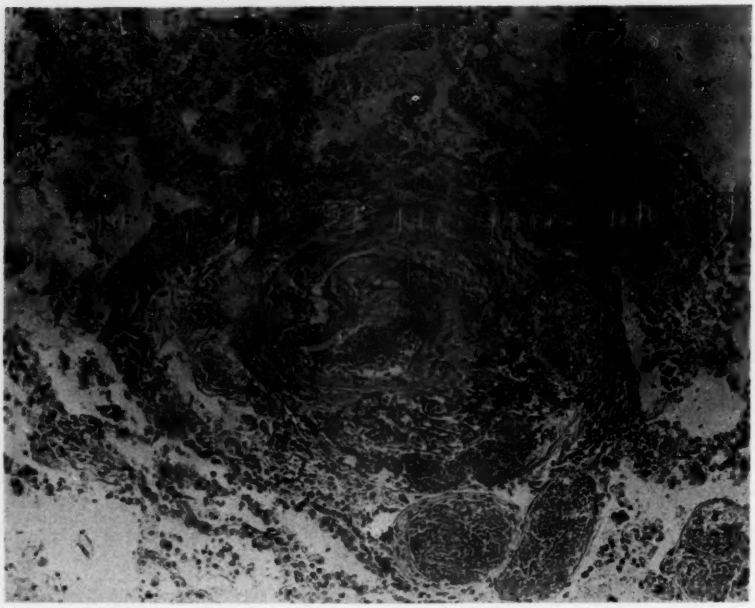

Fig 3 (case 1).—Small branch of pulmonary artery, showing intimal proliferation and recanalization of a thrombus.

Case 2.—A 39 year old woman entered the Stanford service of the San Francisco Hospital on Jan. 1, 1948 because of breathlessness of five days' duration.

She may have been a "blue baby," but in childhood cyanosis was not present. Until the age of 8 years she led a normal life; at that time the parents were advised to restrict her activities because of heart disease. During puberty exertional dyspnea and easy fatigability developed. Cyanosis was first noted in her early twenties and appeared at that time on exertion only. In 1938 she first entered San Francisco Hospital, because of bronchopneumonia. Studies then revealed marked cardiac enlargement, a rough, loud systolic murmur, best heard at the left sternal border and second and third intercostal spaces, and a loud second sound at that area. A roentgenogram showed enlargement of the heart, particularly of the right ventricle, and large pulmonary vessels (fig. 4), observed to be prominently pulsating on fluoroscopic examination. An electrocardiogram showed right axis deviation, with inverted T wave in lead IV. A second entry in 1942 for repair of a strangulated hernia revealed essentially identical findings. On

neither entry was she considered definitely cyanotic. Her erythrocyte count, normal on the first admission, was observed to be elevated during her 1942 admission (5,700,000, with hemoglobin content varying from 114 to 119 per cent on four determinations). Clubbing of digits was not mentioned.

Until 1945 she was able to work as a streetcar conductoress, on her feet for 14 hours a day. Then increasing dyspnea forced her to abandon work, but she was still able to do housework. Persistent cyanosis was present at that time. In January 1947 she reentered San Francisco Hospital because of pregnancy. Examination revealed severe cyanosis and clubbing of fingers. The blood pressure was 140/100. A presystolic gallop was heard over the precordium, and an early diastolic blowing murmur over the left sternal border was audible for the first time. The arm to tongue circulation time was 12 seconds. Fetal death occurred shortly after her admission (see autopsy report), and cesarean section was performed, which was well tolerated. Her condition then improved considerably, and she was able to walk out of the hospital with little dyspnea. During the last year of her life she had moderately severe dyspnea and periodic ankle edema. She was, however, ambulatory until Dec. 27, 1947, when severer dyspnea and

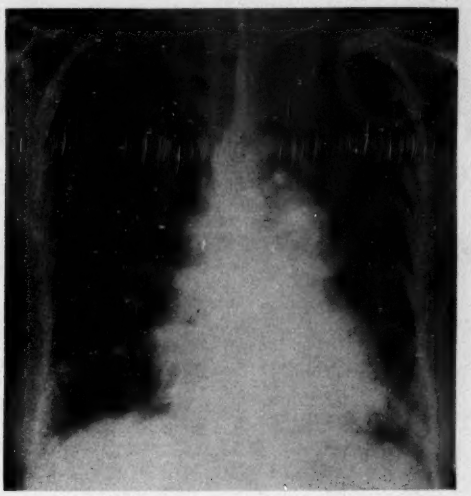

Fig. 4 (case 2).—Roentgenogram of chest showing gross cardiac enlargement with striking prominence of pulmonary artery shadow and enlargement of its branches.

deeper cyanosis developed. She stayed in bed for four days without apparent improvement and then entered the hospital with extreme dyspnea and orthopnea.

Examination revealed a deeply cyanotic woman, perspiring profusely and in severe respiratory distress. The temperature was 38 C. (100.4 F.); the pulse rate was 104, and the blood pressure was 150/100. The veins of the neck were distended, and the lungs were full of moist rales. Auscultation of the heart was unsatisfactory because of respiratory noises. The tender edge of the liver was felt 2 cm. beneath the right costal margin. Pertinent laboratory findings were a hemoglobin concentration of 16 Gm., 5,200 red blood cells and 7,000 white blood cells, with 64 per cent neutrophils. Urinalysis showed a moderate amount of albumin and a few hyaline and granular casts.

The patient was treated with oxygen, digitalis and penicillin but did not respond. Her temperature rose to 39.6 C. (103.3 F.). She died on Jan. 4, 1948.

Anatomic Observations.—Summary: Congenital malformation of the heart; ventricular septal defect with partial slight overriding of the aorta; hypertrophy and dilatation of the heart; dilatation of the pulmonary artery; pulmonary arteriosclerosis and arteriolosclerosis;

local thrombosis of the pulmonary artery; multiple pulmonary emboli with recent infarcts; moderate hyperemia of the viscera; hyperplasia of the bone marrow; thrombosis of the left subclavian vein; edema of the left arm.

Fig. 5 (case 2).—Left ventricular aspect of the ventricular septum. Chordae tendineae of the tricuspid valve are seen across defect. Mild overriding of the aorta is present.

Fig. 6 (case 2).—Intrapulmonary arteriole, showing medial and intimal thickening with almost complete obliteration of lumen.

Heart and Lungs: The heart weighed 600 Gm., and fibrous adhesions extended from the visceral to the parietal pericardium over an area 2 cm. in diameter near the base of the left ventricle. The left ventricle was dilated and moderately hypertrophied. Beneath the aortic valve and involving the membranous septum and adjacent myocardium was an interventricular septal defect, 2.5 cm. broad (fig. 5). No evidence of endocarditis was seen at the margin of

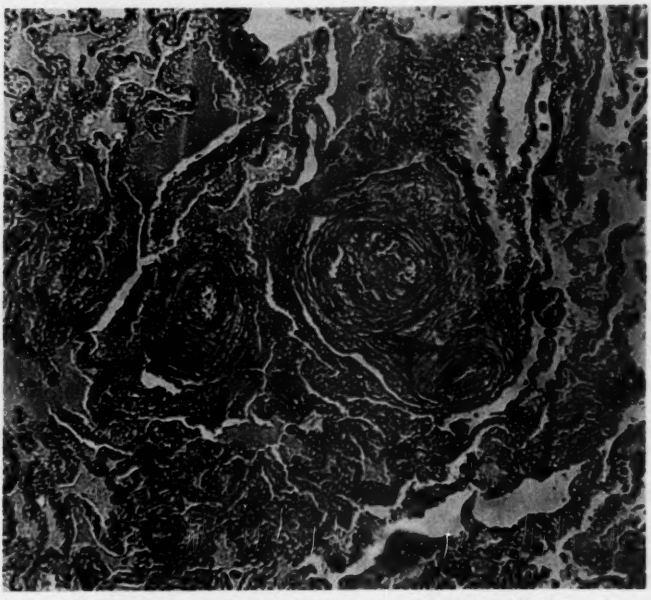

Fig. 7 (case 2).—Intrapulmonary arterioles, showing intimal proliferation and recanalization of a thrombus.

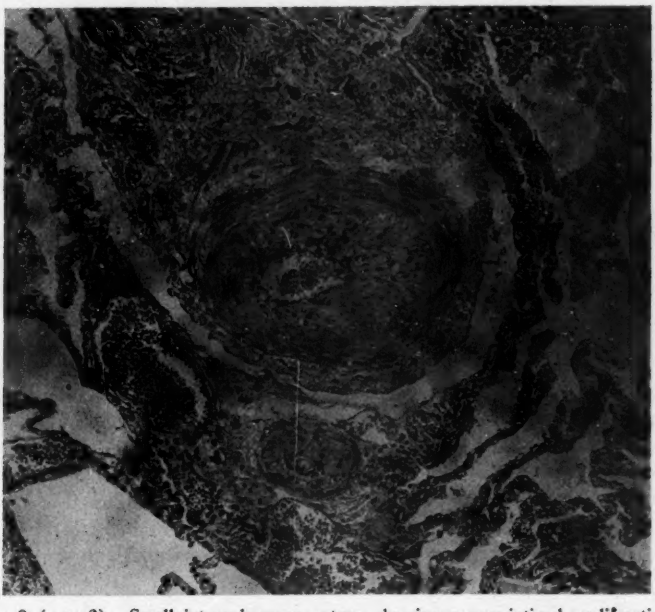

Fig. 8 (case 2).—Small intrapulmonary artery, showing severe intimal proliferation.

the defect, although the endocardium was slightly thickened by fibrous tissue. The degree of dextroposition of the aorta was difficult to ascertain at autopsy. The aortic valve measured 75 mm. in circumference. The right ventricle was dilated and greatly hypertrophied. The circumference of the pulmonary valve was 90 mm. The pulmonary artery was widely dilated and contained many raised yellowish and white intimal spots. An area of yellowish brown roughening was noted in the intima of the pulmonary artery, 2.5 cm. distal to the pulmonary valve. This area measured 2 by 2 cm. and, on sectioning, showed early organization of a thrombus which had developed over an atherosclerotic plaque. The main branches of the pulmonary artery were filled with thrombus material, subtotally occluding the artery to the lower lobe of the left lung. Several distinct recent infarcts were seen in both lungs, with fibrinous deposits being present over the pleural surfaces.

Microscopic Changes in the Pulmonary Vessels: Multiple sections of the lungs showed recent emboli to the pulmonary arterial branches, with areas of recent infarction. Other portions of the lung taken distant to the infarcts showed changes similar to those described in the first case. All different degrees in the severity of structural alterations were seen. Fibrous tissue proliferation in the intima greatly narrowed the lumen of some arterioles (fig. 6), while complete occlusion of the lumen by fibrous tissue was seen in others (fig. 7). Other vessels showed recanalization of thrombi (fig. 8), and, similar to the first case, the pathological alterations were most pronounced in the peripheral portions of the lung.

Heart of the Stillborn Fetus (Jan. 18, 1947): The heart weighed 9 Gm. after fixation in 4 per cent formaldehyde solution. There was practically no pericardial fat. The pulmonary artery and auricular appendages were normal. The foramen ovale was patent, but a thin membranous curtain of tissue covered the opening. The valves were normal. There was a 0.5 cm. triangular defect in the region of the membranous septum between the right and the left ventricles. The right and left ventricles were equal in thickness. The pulmonary artery was continuous with the arch of the aorta in a smooth curve through the ductus arteriosus. The large blood vessels came off the heart in a manner normal for this age of fetus. There was no dextroposition of the aorta nor pulmonary stenosis. The coronary orifices were both moved toward the commissures separating the anterior and left cusps, instead of occupying a position midway between the commissures.

SUMMARY OF OBSERVATIONS IN 35 AUTOPSIED CASES OF THE EISENMENGER COMPLEX

Pertinent anatomic and clinical data on all cases, including our own, are presented in table 1, in which the cases are arranged by age at death in three morphological groups: those fitting the classic concept of the syndrome (group A), those in which the aorta was completely dextroposed (group B) and those complicated by aortic valvular deformities (group C). The second group, that of cases of ventricular septal defect with aorta arising from the right ventricle, is included as representative of the Eisenmenger complex, following the lead of Saphir and Lev.[3a] Further consideration will reveal that this inclusion is justified.

It is seen from the table that three patients survived over the age of 50, but the majority died in the third or fourth decade of life. There were 16 males and 13 females.

Cyanosis was a constant feature, as it was present in groups A and B in all patients, with the exception of one infant and one adolescent. In the majority of cases of group A cyanosis was described as "moderate" in intensity. In most instances in group B it was severe. In 15 cases of group A the age at the onset of cyanosis was reported. It was present from birth or infancy in five cases; it developed in childhood in five and in adolescence or adult life in five. In group B cyanosis was present from birth or infancy in all cases. Group C was thought to be noncyanotic. Cyanosis was specifically stated to be absent in three cases, and in the fourth one it was reported as present in association with severe cardiac failure.

TABLE 1.—*Summary of Pertinent Clinical and Pathological Findings on Thirty-Five Autopsied Cases of Defect of the Ventricular Septum with Dextroposition or Overriding of the Aorta, Arranged in Three Groups by the Age at Death* *

Case No.	Author; Year	Age at Death; Sex	Cyanosis	Clubbing	Polycythemia	Physical Signs	Electrocardiogram	Roentgenographic Finding	Cause of Death	Weight of Heart, Gm.	Septal Defect	Aorta	Wall Thickness R. V.: L. V., Mm.	P. A.	Pulmonary Arteriolar Changes	Miscellaneous
						Group A: Defect of Ventricular Septum with Partial Dextroposition of Aorta										
1	Spitzer,[5a] 1922	Few wk.	.....	....	..	.....	.....	.....	.....	...	Small subaortic defect	Slight overriding	....	Normal trunks	.....	.....
2	Spitzer,[5a] 1922	7 mo.; M	0	....	..	.....	.....	.....	Pneumonia	...	Small subaortic defect	Minimal overriding	....	Normal trunks	.....	.....
3	Ash and others,[5b] 1939	14 mo.	Terminal; mild	....	..	S. M.: midsternal and basal	Moderate R. A. D.	Prominent P. A. region	Pneumonia	...	Basal, 1.1 cm. diameter	Dextroposed	....	Dilated	.....	F. O. open 1 mm.
4	von Rokitansky,[5c] 1875	3 yr.; M	.....	....	..	.....	.....	.....	.....	...	Under right aortic cusp, 4 mm. diameter	Dextroposed	....	Larger than aorta	.....	.....
5	Mahaim, [5d] 1949	6½ yr.; F	Onset at 5 yr.; progressive thereafter	....	..	S. M.: midsternum	Moderate R. A. D.	Gross cardiac enlargement; prominent P. A.	H. F.	330	Oval, 14 mm. longest diameter at membranous septum	Dextroposed	5:11	Dilated	.....	.....
6	Rosedale,[5e] 1935	10 yr.; M	Moderately severe; present since infancy	++	+	S. M.: apex; loud P_2	Slight R. A. D.	.....	Anoxia	310	3 cm. diameter	Dextroposed	....	8 cm.; aorta, 4 cm.	.....	.....
7	Tesseraux,[5f] 1933	12 yr.; M	.....	....	..	.....	.....	.....	Leukemia	...	Oval, 11 × 17 mm.; in anterior septum	Overriding defect	12 15	Dilated	.....	.....
8	Kurtz and others,[5g] 1927	14 yr.; F	Moderately severe since childhood	0	..	S. M. & D. M.: 3d intercostal space, L. S. B.; loud P_2	.....	.....	H. F.	480	Basal	Dextroposed, ¼ over R. V.	15:17	8 cm.; aorta, 7 cm.	.....	.....
9	von Rokitansky,[5c] 1875	15 yr.; M	0	....	..	.....	.....	.....	Endocarditis	...	Subaortic, 1 cm. diameter	Overriding	....	Normal	.....	.....
10	Baumgartner and Abbott,[5h] 1929	21 yr.; M	Mild since age of 13	....	..	S. M. & D. M. at upper L. S. B.	Right B. B. B.	Extreme dilatation of P. A., with increased pulsations	Cerebral abscess	...	2 cm. diameter	Dextroposed	....	Larger than aorta	.....	Hoarseness
11	Dalrymple,[5i] 1848	25 yr.; F	Present since birth	....	..	.....	.....	.....	H. F.	750	Basal	Overriding defect	Hypertrophy of R. V.	.....	.....	.....
12	Wegmüller,[5j] 1949	25 yr.; F	Moderately severe; intermittent since childhood; persistent since 16	++	++	S. M. & D. M.: upper L. S. B.; loud P_2	R. A. D.; diphasic T waves	Dilated P. A., branches; +++ pulsations	Ruptured P. A. aneurysm	330	In membranous septum, 2.5 × 1.5 cm.	Dextroposed	15:10	Dilated; aneurysm	+++	Right-sided aortic arch; F. O. open, slitlike

TABLE 1.—*Summary of Pertinent Clinical and Pathological Findings on Thirty-Five Autopsied Cases of Defect of the Ventricular Septum with Dextroposition or Overriding of the Aorta, Arranged in Three Groups by the Age at Death*—Continued*

Case No.	Author; Year	Age at Death; Sex	Cyanosis	Clubbing	Polycythemia	Physical Signs	Electrocardiogram	Roentgenographic Finding	Cause of Death	Weight of Heart, Gm.	Septal Defect	Aorta	Wall Thickness R. V.: L. V., Mm.	P. A.	Pulmonary Arteriolar Changes	Miscellaneous
13	Eppinger and others,[5k] 1947	27 yr.; F	Moderately severe; onset at 16	++	++	S. M.: over precordium; D. M.: pulmonary area	Marked R. A. D.	Large P. A. and hilar shadows	H. F.	...	Basal	Dextroposed	....	Dilated +++	.....	.....
14	Talley and Fowler,[5b] 1936	31 yr.; F	Since infancy; moderately severe	++	++	S. M.: apex; D. M.: pulmonary area; P_2 ++	.....	Large P. A.; large hilar shadows	H. F.	500	Large	Dextroposed	....	Dilated to twice average size	+++	.....
15	Eisenmenger,[1] 1897	32 yr.; M	Since childhood; prominent	++	..	D. M. at L. S. B.	.....	.....	H. F.	750	.....	Overriding	....	Dilated	.....	.....
16	Millman and Kornblum, [5s] 1936	32 yr.; F	Present; mild	+	+	S. M.: pulmonary area; D. M. at L. S. B.	Slight R. A. D.	.....	S. B. E.	310	.....	Overriding	8:12	Equals aorta	.....	.....
17	Lindeboom,[5o] 1948	33 yr.; F	Since childhood; severe	0	0	S. M. moderately loud at L. S. B.	No axis deviation; notched QRS	Extremely enlarged P. A., hilar shadows, with pulsations	Cerebral thrombosis	700	Subaortic, admits 2 fingers	Overriding: ½ in L. V., ½ in R. V.	....	Dilated	.....	.....
18	Abbott,[5p] 1923	35 yr.; M	Present	+	..	Loud apical S. M.	.....	.....	S. B. E.	...	2 cm. diameter	Slight dextroposition	....	.....	.....	.....
19	Paine and Varco,[5q] 1948	38 yr.; M	Since birth; severe	++	++	No murmurs	R. A. D.	Enlarged heart; prominent P. A. hilar shadows; pulsations	Thoracotomy	...	.....	.....	....	.....	.....	"Eisenmenger complex"; no details given
20	Selzer and Laqueur, 1950, case 2	39 yr.; F	Moderate; since early twenties	++	+	S. M.; variable D. M. at L. S. B.; loud P_2	Slight R. A. D.	Large P. A.; hilar shadows	H. F.	...	2 cm. diameter	Slight overriding	Equal thickness	Dilated ++	+++	.....
21	Schramm,[5r] 1929, case 1	48 yr.; F	Moderate; since 45	....	..	S. M. & D. M.: pulmonary area	.....	.....	H. F.	...	2 cm. diameter; under right and posterior aortic cusp	Overriding: ½ R. V., ½ L. V.	12:20	Dilated ++	.....	.....
22	Selzer and Laqueur, 1950, case 1	57 yr.; M	Moderate; since birth	++	0	S. M.: apex; D. M.: pulmonary area	.....	Large P. A.; large hilar shadows	S. B. E.	...	.....	.....	....	.....	+++	.....
23	Stewart and Crawford,[5t] 1933	60 yr.; F	Moderate; last year of life	0	..	Soft S. M.: apex; loud P_2	.....	.....	H. F.	600	2.5 × 1.5 cm.; under aortic leaflet	Slight dextroposition	Equal thickness	Dilated, larger than aorta	+++	.....

Group B: Ventricular Septal Defect with Complete Dextroposition of Aorta																	
24	Ash and others,[5b] 1939	11 days	Present since 4th day of life	....	..	.....	.....	.....	.....	...	6 mm. defect	Arising from R. V.	....	.....	.....	Patent F. O. and D. A.
25	Ash and others,[5b] 1939	3 mo.	Present	....	..	S. M.: precordium	.....	Enlarged heart	.....	...	5 mm. defect	Arising from R. V.	....	Larger than aorta	.....	Patent F. O.
26	Shapiro,[51] 1930	2 mo.; F	Paroxysmal since birth; later persistent; severe	....	0	.....	.....	.....	H. F.	38	8 mm. diameter	Arising from R. V.	7:6	Larger than aorta	.....	Patent F. O.; only one coronary artery
27	Ash and others,[5b] 1939	9 wk.	Since birth	....	..	None	.....	Prominent P. A.	.....	...	1 cm. diameter	Arising from R. V.	....	Larger than aorta	.....	.....
28	Coyon,[5a] 1897	13 mo.; M	Since birth; mild; terminally severe	....	..	.....	.....	.....	Asphyxia	81	1 × 1.5 cm.	Arising from R. V.	10:15	Large; large branches	.....	.....
29	Saphir and Lev,[54] 1941	21 yr.; M	Since birth	+	..	.....	.....	.....	H. F.	450	2 cm. diameter	Arising from R. V.	12:11	Larger than aorta	.....	Coarctation of aorta
30	von Rokitansky,[5c] 1875	25 yr.; M	Since infancy; severe	....	..	.....	.....	.....	.....	...	Large in anterior septum	Arising from R. V.; small	....	Dilated	.....	.....
31	Schramm,[57] 1929, case 2	58 yr.; M	Since infancy; moderately severe; later, extreme cyanosis	....	+	Soft S. M.: apex	.....	Enlarged heart; very large P. A. and hilar shadows	H. F.	...	2 cm. diameter	Arising from R. V.	Extreme hypertrophy R. V.; 22:10	Extreme dilatation of P. A.	.....	.....
Group C: Defect of Ventricular Septum with Overriding Aorta and Deformity of Aortic Cusps																	
32	Taussig and Semans,[5w] 1940	7 yr.; M	None	....	..	S. M. at base; loud D. M. at L. S. B.	Normal	Enlarged L. V.	Acute endocarditis	...	1.7 cm. diameter	Overriding	Both hypertrophied	Normal	.....	Deformity of right aortic cusp; aortic insufficiency
33	Soulié and others,[5x] 1949	13 yr.; F	None	0	..	Loud S. M. & D. M.: pulmonary area	Evidence of R. V. H. & L. V. H.	Enlarged heart; extreme enlargement of P. A., branches	Thoracotomy	670	Semilunar, 2.5 cm. long	Some dextroposition	Both hypertrophied; 7:20	Dilated +++	.....	Displacement of coronary orifices; aortic cusps deformed
34	Laubry and others [57] 1933	18 yr.; M	Present while in severe H. F.	....	..	Loud S. M. & D. M.: upper L. S. B.	.....	Enlarged heart; prominent P. A.	H. F.	...	1 cm. underneath posterior aortic cusp	Appears dextroposed	L. V. dilated	.....	.....	Deformed posterior aortic cusp
35	Hurst and Schemm,[5z] 1948	22 yr.; F	None	....	..	Loud S. M. & D. M. at base	No axis deviation	Enlarged heart; prominent P. A. and branches; small aorta	H. F.	675	Crescentic, 20 × 6 mm.	Slight overriding (4 mm. over R. V.)	Both hypertrophied; 10:20	Dilated	.....	Right aortic cusp retracted, calcified

* Abbreviations used are R. V., right ventricle; L. V., left ventricle; P. A., pulmonary artery; S. M., systolic murmur; D. M., diastolic murmur; R. A. D., right axis deviation; H. F., heart failure; L. S. B., left sternal border; S. B. E., subacute bacterial endocarditis; F. O., foramen ovale; P_2, pulmonary second sound; B. B. B., bundle branch block, and D. A., ductus arteriosus. R. V. H. and L. V. H. indicate right and left ventricular hypertrophy, respectively. 0 indicates absence of a sign; the severity of various findings are graded +, mild; ++, moderate; +++, severe.

Auscultatory findings were reported in 24 cases. In two cases no murmurs were found; in one a diastolic murmur only was noted. In all other cases systolic murmurs were present but were variable in intensity, quality, location and conduction. The loud systolic murmur at the fourth left costal cartilage characteristic of the isolated ventricular septal defect was infrequently encountered. In groups A and B there was a frequent association of the systolic murmur with a diastolic murmur, which almost always was described as early diastolic blowing murmur best heard at the left sternal border. In group C, of course, loud diastolic murmurs characteristic of aortic insufficiency were present. As a rule, in the cases of the Eisenmenger complex there was a loud second sound present in the pulmonary area.

Electrocardiographic reports indicate that right axis deviation, the pattern of right ventricular hypertrophy or a right bundle branch block was, as a rule, present. Exceptions were rare and usually accountable for by complications.

The roentgenographic appearance of the cardiac shadow in this series showed a remarkable uniformity. Of the 17 instances in which roentgenograms were described or reproduced, enlargement of the pulmonary artery was observed in 16. The one exception was in the case of a child in whom severe aortic insufficiency was present, which may have been a clinically more significant lesion than the Eisenmenger complex. The pulmonary artery shadow and that of its branches were usually described as prominently enlarged, often extreme in degree. Pronounced hilar pulsations were usually noted on fluoroscopy, and the pulmonary fields showed varying degrees of congestion, often severe. The heart was almost always enlarged.

The commonest cause of death in the series was heart failure, with infectious endocarditis next.

Pathological features of the Eisenmenger complex were as follows: cardiac hypertrophy, almost uniformly affecting the right ventricle, a large basal ventricular septal defect, varying degree of dextroposition of the aorta and dilatation of the pulmonary arterial trunk to aneurysmal proportions.

The defect of the ventricular septum was always located in the typical area, involving the membranous septum, its anterior part or the muscular septum just anterior to it. Its shape was usually oval, occasionally crescentic or round. The size of the defect varied from 1 to 3 cm. in the longest diameter in the fully grown heart. Since the size of the defect is of crucial importance from the standpoint of pathogenesis of the malformation and its hemodynamic effect, it was thought of importance to compare the size of the defect with that of defects unassociated with other malformations (Roger's disease) and those associated with dextroposition of the aorta and pulmonary stenosis (tetralogy of Fallot). For that purpose the previously reported series of uncomplicated ventricular defects [4] and of the tetralogy of Fallot [6] were consulted. The sizes of the defects in these three syndromes in the fully grown heart are presented in table 2. It is seen that the majority of uncomplicated defects of the ventricular septum are small; in the Eisenmenger complex moderate-sized defects occur. With the exception of the rare isolated defects in the lower septum, the location and shape of the defects in the three

6. Selzer, A.; Carnes, W. H.; Noble, C. A., Jr.; Higgins, W. H., Jr., and Holmes, R. S.: The Syndrome of Pulmonary Stenosis with Patent Foramen Ovale, Am. J. Med. **6**:3 (Jan.) 1949.

syndromes are identical. It should be emphasized that the largest defect in the ventricular septum encountered in any case of these syndromes occupies only a small portion of the septum, probably less than 10 per cent of its surface in the fully grown heart. There is no gradual transition between larger defects of the ventricular septum and the complete absence of the septum.

The position of the aorta in relation to the septal defect has been usually reported as "overriding." In some cases the degree of dextroposition of the aorta was estimated, and it is seen that all degrees of transition may be found, from cases in which the aorta originates almost entirely from the left ventricle to those in which it is completely dextroposed, i. e., originates from the right ventricle.

The other two features of the Eisenmenger complex, dilatation of the pulmonary artery and hypertrophy of the right ventricle, were consistently present throughout the series. In addition to our two cases in which microscopic vascular changes in the lungs were reported in detail, three other cases were described as having shown serious changes in the pulmonary arterioles.

TABLE 2.—*Size of Defect of Ventricular Septum in Fully Grown Heart in Uncomplicated Ventricular Septal Defects, the Eisenmenger Complex and the Tetralogy of Fallot*

Size of defect, cm.	Less Than 1 (Largest Diameter)	1 to 2	2 to 3
		No. of Cases	
Uncomplicated ventricular septal defect	20	7	3
Eisenmenger's complex	..	9	3
Tetralogy of Fallot	..	4	10

COMMENT

Morphological Relationship of the Eisenmenger Complex to the Uncomplicated Defect of the Ventricular Septum.—It has been shown that the secondary features of the Eisenmenger complex, the dilatation of the pulmonary artery and the hypertrophy of the right ventricle, are consistently observed in large, simple defects of the ventricular septum.[4] The morphological distinction between the latter and the Eisenmenger complex, based on the presence or absence of dextroposition of the aorta, may present more difficulty at the autopsy table than is generally appreciated. It is of interest to note that Eisenmenger [1] reported his original case as one of a ventricular septal defect and in a later article [7] clarified his position concerning the overriding of the aorta. He presented evidence that the aorta is normally located in such a relation to the ventricular septum that if the membranous portion of the latter is defective it comes in contact with both ventricles (fig. 9*A*). Thus, he believed that overriding of the aorta is a normal by-product of a large ventricular septal defect and not a developmental dextroposition. The unity of the two syndromes has been accepted in the German literature.[8]

7. Eisenmenger, V.: Ursprung der Aorta aus beiden Ventrikeln beim Defect des Septum ventriculorum, Wien. klin. Wchnschr. **11**:25, 1898.

8. Müller, H.: Zur Klinik und pathologischen Anatomie des unkomplizierten, offenen Septum ventriculorum, Deutsches Arch. f. klin. Med. **133**:316 (Sept.) 1920; Ein Fall von unkompliziertem offenem Septum ventriculorum cordis (maladie de Roger) mit grosser Lücke, Schweiz. med. Wchnschr. **67**:289 (April 3) 1937. Seiler, S.: Ueber einen Fall von Vitium cordis congenitum (Ventrikelseptumdefekt + Pulmonalinsuffizienz), Helvet. med. acta **6**:357 (July) 1939. Wegmüller.[5]

In order to account for the morphological similarity between larger ventricular septal defects with or without the dextroposition of the aorta, and in consideration of the generally accepted fact that the aorta may be embryologically malposed in such cases, a different way of unifying the two syndromes has been suggested.[4] It was thought that the same process of maldevelopment (Spitzer [5a]) which brings about transposition of the arterial trunks in its severest form, and is responsible

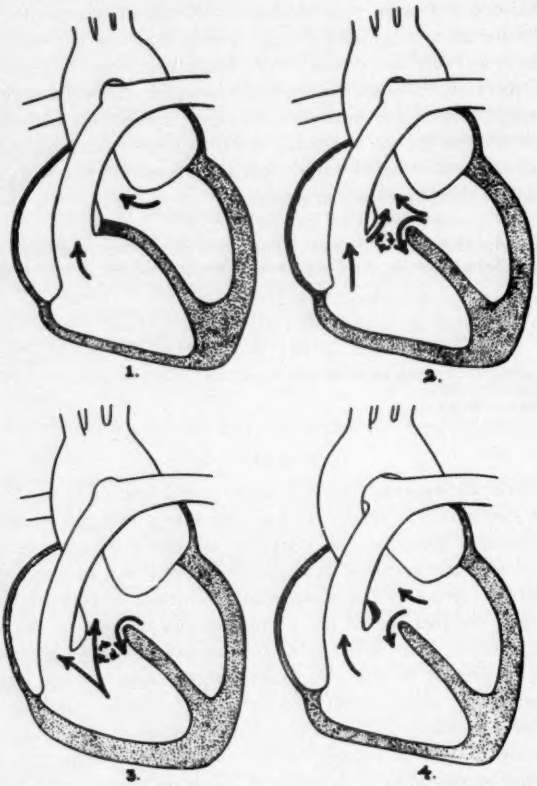

Fig. 9.—Semidiagrammatic presentation of the topography of the great vessels as it would appear on a coronal section of the heart at the level of the membranous septum, with arrows indicating the probable path of the circulation. *1.* Normal heart showing the relationship of the aortic orifice to the right ventricle. If the membranous septum (shaded area) was defective, the aorta would come in close contact with the right ventricle (von Rokitansky, Eisenmenger) acquiring an "overriding" position. *2.* Eisenmenger's complex with mild overriding of the aorta. The entry of venous blood into the aorta is due to the turbulence. *3.* Eisenmenger's complex with severe dextroposition of the aorta. Systemic circulation is maintained by the right ventricle. *4.* A correction of the aortic overriding by deformity of the posterior or right aortic cusp (Soulié and his associates); in spite of dextroposition of the aorta the circulation is that of a pure ventricular septal defect.

for partial dextroposition of the aorta (overriding) with or without pulmonary stenosis in less severe forms, causes the isolated high ventricular septal defect in

its mildest form. This view finds further support in the present study. 1. It was shown that within the Eisenmenger complex all degrees of dextroposition of the aorta can be found. 2. The otherwise identical defects are, on the average, larger in the Eisenmenger complex (or tetralogy of Fallot) than in the uncomplicated form (table 2). 3. A striking example is presented in our case 2 in which the fetus had a defect of the ventricular septum appearing identical with that of the mother, except for the dextroposition of the aorta, which was present in the mother but not in the fetus. Yet it was the fetus that had an abnormal origin of the coronary ostiums, which is considered characteristic for the transposition malformations.

Although Eisenmenger's original interpretation appears in part incorrect, his observation helps to emphasize the difficulty which is often encountered at autopsy in deciding whether or not dextroposition of the aorta was present during life. It is highly probable that the "physiological" overriding of the aorta can be accentuated by changes in pressure relationship, in topography of the arterial trunks related to gradual dilatation of the pulmonary artery and in other factors. Thus, overriding of the aorta need not be considered a fixed morphological feature.

Pulmonary Vascular Changes and Their Relation to Cyanosis.—Recently, there has been growing interest in pulmonary arteriolar changes associated with congenital heart disease. Welch and Kinney [9] and Edwards and his co-workers [10] reported studies of pulmonary arteriolar changes in cases of septal defect and patency of the ductus arteriosus. Rich [11] described thrombotic changes associated with tetralogy of Fallot, which were confirmed by Hales and Liebow.[12]

Both our cases showed severe changes in pulmonary arterioles, which were also mentioned in descriptions of three other cases. The uniform finding of pulmonary hypertension in cases of the Eisenmenger complex studied by cardiac catheterization suggests that these changes are an essential part of the syndrome; it was shown also that the pulmonary arteriolar resistance is extremely high.[13]

The reported changes in the pulmonary arterioles (figs. 3, 6, 7 and 8) belong pathologically to the same group as those found frequently in other conditions associated with pulmonary arterial hypertension (mitral stenosis, cor pulmonale) and those associated with large pulmonary arterial flow (septal defects, patent ductus arteriosus). The changes in the intima and media show some similarity to

9. Welch, K. J., and Kinney, T. D.: The Effect of Patent Ductus Arteriosus and Intra-auricular and Interventricular Septal Defect on the Development of Pulmonary Lesions, Am. J. Path. **24**:729 (July) 1948.

10. Edwards, J. E.; Douglas, J. M.; Burchell, H. B., and Christensen, N. A.: Pathology of Intrapulmonary Arteries and Arterioles in Coarctation of the Aorta Associated with a Patent Ductus Arteriosus, Am. Heart J. **38**:205 (Aug.) 1949.

11. Rich, A. R.: A Hitherto Unrecognized Tendency to the Development of Widespread Pulmonary Vascular Obstructions in Patients with Congenital Pulmonary Stenosis (Tetralogy of Fallot), Bull. Johns Hopkins Hosp. **82**:389 (March) 1948.

12. Hales, M. R., and Liebow, A. A.: Collateral Circulation to the Lungs in Congenital Pulmonic Stenosis, Bull. Internat. A. M. Mus. **28**:1 (Oct.) 1948.

13. (*a*) Bing, R. J.; Vandam, L. D., and Gray, F. D.: Physiological Studies in Congenital Heart Disease: III. Results Obtained in 5 Cases of Eisenmenger's Complex, Bull. Johns Hopkins Hosp. **80**:323 (June) 1947. (*b*) Dexter, L.: Pulmonary Circulatory Dynamics in Health and Disease, at Rest, Bull. New England M. Center **9**:240 (Dec.) 1949.

systemic arteriolar changes in systemic hypertension. In severer cases of pulmonary arteriolar disease changes resemble those of malignant hypertension.[14]

From the physiological standpoint, it is clear that the pulmonary arteriolar changes represent evidence of long-standing severe pulmonary hypertension. It has been suggested, however, by Burwell,[15] Taussig and Blalock [16] and Taussig [17] that pulmonary vascular disease interferes with oxygen exchange in the lungs and thus is responsible for the cyanosis. This opinion was based on considerations that oxygen inhalation raised the arterial oxygen content and that in the Eisenmenger complex the circulation to the lungs is not "inadequate." Yet, neither of these factors helps in determining the mechanism of cyanosis.[18] There is no valid reason to separate the Eisenmenger complex from all other forms of congenital heart disease with cyanosis, in which it is evident that anoxemia is caused by an admixture of venous blood in the systemic circulation. On the contrary, one can present evidence that in the Eisenmenger complex caval blood enters the aorta; this is shown by hemodynamic studies and by angiocardiography. Moreover, a causal relationship between pulmonary hypertension and arteriolar disease on one hand and cyanosis and anoxemia on the other has not been definitely established.[18] Finally, Bing and his associates [13a] interpreted the finding of a close check between blood flow determinations in the Eisenmenger complex performed by the oxygen and carbon dioxide methods as evidence of a normal pulmonary oxygen exchange.

One can further cite the case of Soulié and his collaborators [5x] as illustrating the lack of relationship between cyanosis and the pulmonary factors. In spite of proved severe pulmonary hypertension and arteriolar disease, the arterial oxygen saturation was normal, as apparently the coexisting aortic insufficiency "corrected" the overriding of the aorta to a point that caval blood could not enter it.

It seems reasonable to believe that anoxemia and cyanosis in the Eisenmenger complex are due to a "shunt mechanism" and that pulmonary venous blood is fully oxygenated, such as is shown directly in tetralogy of Fallot and the anoxemic form of atrial septal defect. [19]

Circulatory Dynamics of the Eisenmenger Complex.—A discussion of the hemodynamics of Eisenmenger's complex can best be opened by summarizing facts about which there appears to be reasonable certainty.

1. Pathological facts: (*a*) The defect of the ventricular septum is always located in the basal, subaortic portion of the septum and occupies only a minute portion of the septum, with most of it intact. (*b*) The aorta may originate mostly

14. Parker, F., Jr., and Weiss, S.: The Nature and Significance of Structural Changes in the Lungs in Mitral Stenosis, Am. J. Path. **12**:573 (Sept.) 1936.

15. Burwell, S. C.: Studies of the Circulation in Congenital Affections of the Heart and Their Application to Some of the Problems of Heart Disease, Tr. & Stud., Coll. Physicians, Philadelphia **10**:82 (June) 1942.

16. Taussig, H. B., and Blalock, A.: Observations on the Volume of the Pulmonary Circulation and Its Importance in the Production of Cyanosis and Polycythemia, Am. Heart J. **33**:413 (April) 1947.

17. Taussig, H. B.: Congenital Malformations of the Heart, New York, Commonwealth Fund, 1947.

18 Selzer, A.: Chronic Cyanosis, Am. J. Med., to be published.

19. Selzer, A., and Lewis, A. E.: The Occurrence of Chronic Cyanosis in Atrial Septal Defect, Am. J. M. Sc. **218**:516 (Nov.) 1949.

from the left ventricle, may arise mostly from the right ventricle or may occupy an intermediate position. All degrees of transition can be found between the two extreme positions. (*c*) Pulmonary vascular changes indicative of high arteriolar resistance can usually be demonstrated.

2. Clinical facts: (*a*) Systolic pressures in the right ventricle and the pulmonary artery are equal and are always elevated in the Eisenmenger complex but are occasionally normal in simple ventricular septal defect. This is shown by a collection of results of cardiac catheterization presented in table 3.[20] (*b*) In many cases, perhaps the majority, the pressure elevation in the right ventricle–pulmonary artery system is such that systolic pressure readings are identical with the pressure readings in the aorta and the left ventricle. (*c*) Increased oxygenation of pulmonary arterial blood and decreased oxygenation of systemic arterial blood prove that there is a cross shunt, or free mixing, of caval and pulmonary venous blood. The systemic flow may equal the pulmonary flow, or one may exceed the other, without any consistency in this relationship.

3. Experimental facts: Studies on experimental defects of the ventricular septum [21] show that a fistulous connection between the two ventricles of a dog's heart comparable to a medium-sized human ventricular septal defect results in flow of blood through the fistula from the higher-pressured left ventricle to the lower-pressured right ventricle. No equalization of pressure in the two chambers takes place, but a slight fall in the left and a rise in the right ventricular systolic pressure occur.

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20. (*a*) Lagerlöf, H.; Mannheimer, E., and Werko, L.: Heart Catheterization in Morbus Ceruleus, Bibliot. Cardiol. **4**:193, 1949. (*b*) Bing and others.[18a] (*c*) Holling, H. E., and Zak, G. A.: Cardiac Catheterization in Congenital Heart Disease, Brit. Heart J. **12**:153 (April) 1950. (*d*) Hultgren, H. N.: Unpublished observations. (*e*) Dexter, L.: Cardiac Catheterization in the Diagnosis of Congenital Heart Disease, Bull. New York Acad. Med. **26**:93 (Feb.) 1950. (*f*) Griffith, G. C.; Cosby, R. S., and Levinson, C. D.: Cardiac Catheterization in Adult Congenital Heart Disease, California Med. **72**:431 (June) 1950. (*g*) Cournand, A.; Baldwin, J. S., and Himmelstein, A.: Cardiac Catheterization in Congenital Heart Disease, New York, Commonwealth Fund, 1949. (*h*) Dexter, L.; Haynes, F. W.; Burwell, C. A.; Eppinger, E. C.; Sosman, M. C., and Evans, J. M.: Studies of Congenital Heart Disease: III. Venous Catheterization as a Diagnostic Aid in Patent Ductus Arteriosus, Tetralogy of Fallot, Ventricular Septal Defect and Auricular Septal Defect, J. Clin. Investigation **26**:561 (May) 1947. (*i*) Handelsman, J. C.; Bing, R. J.; Campbell, J. A., and Griswold, H. E.: Physiological Studies in Congenital Heart Disease: V. Circulation in Patients with Isolated Septal Defects, Bull. Johns Hopkins Hosp. **82**:615 (June) 1948. (*j*) Burchell, H. B.; Taylor, B. E.; Pollack, A. A.; DuShane, J. W., and Wood, E. H.: Symposium on Cardiac Catheterization: Ventricular Septal Defect and Pulmonary Hypertension Without Hypoxemia, Proc. Staff Meet., Mayo Clin. **23**:507 (Oct. 27) 1948. (*k*) Baldwin, E. D.; Moore, L. V., and Noble, R. P.: The Demonstration of Ventricular Septal Defects by Means of Right Heart Catheterization, Am. Heart J. **32**:152 (Aug.) 1946. (*l*) Morgan, E. H., and Burchell, H. B.: Ventricular Septal Defect Simulating Patent Ductus Arteriosus, Proc. Staff Meet., Mayo Clin. **25**:69 (Feb. 1) 1950.

21. Holman, E., and Beck, C. S.: Physiological Response of Circulatory System to Experimental Alterations: Effect of Intracardiac Fistulae, J. Exper. Med. **42**:681 (Nov.) 1925. Eppinger, E. C., and Gross, R. E.: Measurements of the Circulation in Dogs with an Interventricular Septal Defect, J. Clin. Investigation **20**:461 (July) 1941. Dillon, W. H., and Schreiber, H., Jr.: Cardiodynamics of Experimental Interventricular Communication, Am. J. Physiol. **154**:281 (Aug.) 1948. Hawley, J. G.; Little, R. C., and Feil, H.: Further Studies of the Cardiodynamics of Experimental Interventricular Communications, Circulation **1**:321 (March) 1950.

It is seen from the foregoing summary that the most characteristic feature of Eisenmenger's complex is the presence of severe pulmonary hypertension, which is invariably demonstrated in this syndrome, in contrast to the atrial septal defect, the ventricular septal defect and the patent ductus arteriosus, where it is only occasionally present. The consistency in the observation of severe pulmonary hypertension and the frequency with which equal pressures in the two arterial trunks are demonstrated indicate that increased pulmonary resistance plays an important role in the dynamics of the circulation of the Eisenmenger complex.

TABLE 3.—*Comparative Pressures in Systemic and Pulmonary Circulation Obtained by Cardiac Catheterization in Cases Diagnosed Clinically as Eisenmenger's Complex and Defect of the Ventricular Septum*

Author	Age, Yr.	Pressures, Mm. Hg				Arterial Oxygen Saturation, %
		Right Ventricle	Pulmonary Artery	Aorta	Systemic Artery	
1. The Eisenmenger Complex						
Lagerlöf and others [20a]	5	117/6	120/51	.....	115/70	88
Bing and others [18a]	9	137/12	(m)100	.....	(m)100	83
Lagerlöf and others [20a]	10	98/8	98/54	100/56	.....	76
Lagerlöf and others [20a]	10	109/0	109/14	.....	135/90	76
Bing and others [18a]	19	97/36	122/82	.....	134/82	77
Holling and Zak [20c]	23	95/0	95/55	.....	130/80	77
Hultgren [20d]	24	85/5	81/45	105/80	125/83	80
Bing and others [18a]	25	112/0	112/64	.....	122/79	77
Dexter [20e]	..	117/1	116/72	.....	117/72	..
Griffith and others [20f]	29	99/2	102/60	.....	115/70	82
2. Ventricular Septal Defect						
Cournand and others [20g]	3	39/6	36/15	92/48	.....	95
Dexter and others [20h]	6	29/4	29/12	.....	105/45	100
Hultgren [20d]	6	32/5	32/9	.....	93/40	95
Handelsman and others [20i]	9	32/8	30/10	.....	105/61	91
	10	40/29	20/29	.....	155/71	99
Cournand and others [20g]	12	89/9	85/48	.....	188/84	97
Burchell and others [20j]	12	106/10	106/60	.....	110/78	97
Baldwin and others [20k]	16	54/29	.....	.....	118/70	98
Baldwin and others [20k]	20	40/10	.....	.....	112/72	91
Hultgren [20d]	23	39/8	38/11	115/80	.....	94
Morgan and Burchell [20l]	34	67/9	54/21	.....	133/54	95

It has recently become apparent that in certain anomalies of the heart pulmonary hypertension may have to be present from birth as a condition for the survival of the patient.[22] The reason for this is the fact that the physiological postnatal adjustment, during which an equal pressure in the pulmonary artery and the aorta changes into a high resistance and high pressure systemic circulation and a low resistance and low pressure pulmonary circulation,[23] could prove fatal in those cases in which both trunks originate from a common source. The malformation in such a case creates a pressure pump which has two outlets; the quantity of blood entering

22. Douglas, J. M.; Burchell, H. B.; Edwards, J. E.; Dry, T. J., and Parker, R. L.: Systemic Right Ventricle in Patent Ductus Arteriosus: Report of a Case with Obstructive Pulmonary Vascular Lesions, Proc. Staff Meet., Mayo Clin. **22**:413 (Sept. 17) 1947. Hamilton, W. F.; Winslow, J. A., and Hamilton, W. F., Jr.: Note on a Case of Congenital Heart Disease with Cyanotic Episodes, J. Clin. Investigation **29**:20 (Jan.) 1950.

23. Hamilton, W. F.; Woodbury, R. A., and Wood, E. B.: The Relation Between Systemic and Pulmonary Blood Pressure in the Fetus, Am. J. Physiol. **119**:206 (May) 1937.

each of them is in inverse proportion to the resistance offered. Thus, a low resistance pulmonary outlet could draw all the blood, with none available for the high resistance systemic circulation. In such cases survival depends on equal resistance in the pulmonary and systemic circuits, which can be achieved by (*a*) systemic hypotension or pulmonary hypertension or by (*b*) a mechanical obstruction of the low resistance outlet, as pulmonary stenosis. The obvious conditions to which this concept of a "double outlet ventricle" applies are partial transposition of the arterial trunks, in which both great vessels originate from the right ventricle, and the trilocular heart, in which both trunks arise from a common ventricle. A somewhat similar situation exists in some cases of patent ductus arteriosus associated with coarctation of the aorta,[10] in which the right ventricle maintains the pulmonary circulation and the lower part of the systemic circulation.

It is obvious that in the variant of the Eisenmenger complex with complete dextroposition of the aorta (group B, table 1) one is dealing with a "double outlet ventricle" in which pulmonary arteriolar constriction and/or disease has to be present from birth for survival, since no protective pulmonary stenosis is present. However, in the classic Eisenmenger complex, where the aorta is merely overriding the septal defect, one has to search for another factor explaining the pulmonary hypertension.

It was shown that an experimental ventricular septal defect[21] produces a pathway for a left to right shunt. One can assume, however, that as the defect in the ventricular septum becomes larger and approaches the size of the aortic orifice the left ventricle becomes a "double outlet ventricle," in which case the low resistance right ventricle can draw all the blood away from the systemic circulation, unless the resistance in the right side of the heart is raised either by pulmonary stenosis or by pulmonary arteriolar constriction and hypertension. Pressure relationships between the two ventricles in cases of Eisenmenger's complex and Fallot's tetralogy suggest that in the majority of them the defect is in effect large enough to make the left ventricle a "double outlet ventricle."

The concept of the "double outlet ventricle" as applied to the Eisenmenger complex, the trilocular heart and other similar syndromes is based on fundamental principles of hemodynamics and has to be postulated to explain the fact that survival in the postembryonic life is at all possible with some of these malformations. However, the mechanism of the production of the protective pulmonary hypertension in such cases, the stimulus for the development of pulmonary arteriolar constriction and/or disease from infancy, is as yet unknown.

Another problem requiring analysis is that of the physiological significance of the overriding aorta. It is commonly assumed that an "overriding aorta collects blood from both ventricles." Such a statement ignores the fact that normally the systolic pressure in the right ventricle is lower than the diastolic pressure in the aorta, and, if normal relationships were preserved, blood could not ordinarily flow from the right ventricle to the aorta. Deoxygenated caval blood can enter the aorta (*a*) if the systemic circulation is maintained by the right ventricle in complete dextroposition of the aorta (fig. 9, diagram 3); (*b*) if pressures in the two ventricles are equal, in which case the overriding position of the aorta facilitates turbulence and mixing of blood in the defect (fig. 9, diagram 2); (*c*) if the pressure

in the right ventricle is slightly lower than in the left, in which case turbulence may still throw right ventricular blood into the aorta, perhaps aided by the Venturi phenomenon.[24]

The importance of the topographic relationship of the aorta to the ventricular septal defect in the production of anoxemia is exemplified by observations of Soulié and his associates[5a] in their cases of the Eisenmenger complex associated with aortic valvular deformity. In one such case the aorta was seen at autopsy to be dextroposed over the septal defect, so that morphologically this was an instance of Eisenmenger's complex, but the longitudinal axis of the aorta was observed to be rotated counterclockwise, probably as a result of changes brought on by aortic valve deformity and insufficiency (fig. 9, diagram 4). This shift corrected the overriding position of the aorta, and the patient was found to have a normal oxygen saturation, even though severe pulmonary hypertension was present. Significantly, two other patients with the Eisenmenger complex associated with aortic insufficiency (table 1, group C) were noncyanotic, which adds great weight to the observations and explanation of Soulié and his co-workers.

Clinical Features of the Eisenmenger Complex.—A review of the pertinent features of the autopsied cases reveals that the clinical picture of this syndrome is well defined. It was shown that the late development of cyanosis has been overemphasized. In all cases with complete dextroposition of the aorta cyanosis was present from birth or infancy and was severe; in those with partial dextroposition of the aorta it frequently developed in infancy or childhood, not unlike the cyanosis of the tetralogy of Fallot. The degree of cyanosis was, however, on the whole less severe than in the tetralogy of Fallot, and higher degrees of polycythemia with prominent clubbing of digits were less frequently encountered in the Eisenmenger complex. Cyanosis was usually not present in cases associated with aortic insufficiency, and for that reason it was suggested that this combination be classified as the simple ventricular septal defect with aortic regurgitation.

Pulmonary hypertension appears to be a constant and important feature of the Eisenmenger complex. This may be demonstrated by direct pressure measurement or suggested by the striking dilatation of the shadow of the pulmonary artery and its branches in the roentgenogram, usually associated with intense pulmonary congestion and large amplitude of pulmonary vascular pulsations. This is also supported by the constant finding of the pattern of right ventricular hypertrophy in the electrocardiogram.

Murmurs in the Eisenmenger complex seem to be less characteristic than in uncomplicated ventricular septal defect. Systolic murmurs, often loud and harsh, are usually present and vary in location. Early diastolic murmurs at the left border of the sternum are common and are probably due to relative pulmonary insufficiency. Very loud diastolic murmurs, almost continuous, and changes in systemic pulse pressure have been reported in cases associated with aortic valve deformity. As a rule, the second sound in the pulmonary area is prominently accentuated.

The prognosis of the Eisenmenger complex appears to be fair and is comparable to that of other congenital defects of the less serious type. The average patient

24. Wiggers, C. J.: Physiology in Health and Disease, ed. 4, Philadelphia, Lea & Febiger, 1944, p. 564.

survives to early or middle adult life. Heart failure and bacterial endocarditis are important causes of death.

Definition of the Eisenmenger Complex.—From the foregoing clinical, physiological and pathological analysis of the Eisenmenger complex, it appears that an exact definition of the syndrome presents some difficulty. The classic description of the syndrome as cited in the introduction is inaccurate because of the uncertainty of deciding what "overriding of the aorta" is. It has been mentioned that in the absence of the membranous septum the aorta physiologically "overrides" the defect. On the other hand, dextroposition of the aorta observed at the autopsy table need not be considered as evidence of its physiological significance during life. One can state that an overriding aorta is of functional significance if, in the presence of favorable pressure relationships between the ventricles, it facilitates turbulence and mixing in the septal defect, permitting an admixture of caval blood to enter the aorta. Thus, a clinically significant overriding of the aorta exists in those cases in which there is lowered arterial oxygen saturation. It should be emphasized that the presence of anoxemia is much more reliable and sensitive evidence for the presence of an overriding aorta than the early opacification of the aorta by angiocardiography [25] or a shortened circulation time. Both these tests depend on a short circuiting of foreign substances flowing with the caval blood into the aorta, but these substances have to be present in relatively high concentrations to become demonstrable.

The Eisenmenger complex merges inconspicuously with the simple ventricular septal defect. The dividing line is a clinical feature, namely, the completeness of oxygen saturation of the arterial blood. The hemodynamic similarities of the two syndromes are shown in table 3.

On the other extreme of the spectrum, one may find it difficult to separate some cases of the Eisenmenger complex from those of the tetralogy of Fallot, especially the ones with milder degrees of pulmonary stenosis. There may be transitional forms in which it is difficult to classify a case as belonging to one or the other category.

With the increasing knowledge of hemodynamics of congenital heart disease, definitions of syndromes based purely on morphological criteria become unsatisfactory. Both physiological and pathological facts have to be considered in the definition of a congenital cardiac disease entity. In the case of Eisenmenger's complex it is suggested that the concept of "dextroposition of the aorta" be considered from the clinical, as well as the anatomic, standpoint. Only those cases in which the dextroposition of the aorta is functioning, i. e., permitting venous blood to enter the aorta, should be included as instances of the complex. Cases with normal arterial oxygen saturation should be excluded and considered as instances of simple ventricular septal defect. Thus, one can define the Eisenmenger complex as one in which the following criteria are fulfilled: (*a*) a high, localized defect of the ventricu-

25. Ulfsparre, F.: Angiocardiography in Morbus Ceruleus, Bibliot. Cardiol. **4**:140, 1949. Donzelot, E.; Eman-Zadé, A. M.; Heim de Balsac, R., and Kolosy, M.: Le complexe d'Eisenmenger: Etude de 29 cas, Arch. d. mal. du coeur, vol. 42, supp. 1, p. 138. Moller, T.: Circulation Time Studies by Fluoroscein Method Especially in Morbus Ceruleus, Bibliot. Cardiol. **4**:171, 1944.

lar septum, (*b*) a position of the aortic orifice in relation to the defect which permits an admixture of venous blood to enter the aorta, as evidenced by anoxemia, and (*c*) an absence of significantly elevated resistance at the pulmonary outflow tract of the right ventricle. Secondary features of the syndrome, not included in the definition, but constantly found in the entity are (*a*) strikingly elevated resistance at the pulmonary arterioles with organic changes within them; (*b*) severe pulmonary hypertension or even equalization of pressure in the two circulations; (*c*) hypertrophy of the right ventricle; (*d*) dilatation of the pulmonary artery and its branches.

SUMMARY AND CONCLUSIONS

Two new cases of the Eisenmenger complex in adults are reported in detail. In addition, data on 33 autopsied cases of this syndrome are tabulated and their clinical and pathological features reviewed. Following the lead of Saphir and Lev, the concept of the Eisenmenger complex is widened to include cases in which the aorta is completely dextroposed, arising from the right ventricle.

Clinical features of the Eisenmenger complex include cyanosis, which is frequently present from birth; noncharacteristic systolic and diastolic murmurs with a loud pulmonary second sound; roentgenologic evidence of striking dilatation of the pulmonary artery and its branches, associated with pulmonary congestion and increased arterial pulsations, and evidence of right ventricular enlargement and hypertrophy in the roentgenogram and electrocardiogram.

Pathological features of the Eisenmenger complex include a localized high defect of the ventricular septum, usually oval or crescentic, measuring between 1 and 2.5 cm. in longest diameter; varying degrees of dextroposition of the aorta, from minimal overriding to a complete origin of the aorta from the right ventricle; dilatation of the pulmonary artery and its branches, and severe hypertrophy of the right ventricle, with or without some left ventricular hypertrophy.

Microscopic examination of the pulmonary arterioles in our two cases revealed severe intimal and medial changes. Such changes have also been noted by others, and it is believed that they constitute a characteristic feature of the Eisenmenger complex, being evidence of long-standing severe pulmonary hypertension.

Further evidence is presented to support the view that no dividing line exists between the uncomplicated defect of the ventricular septum and the Eisenmenger complex, and that both are caused by varying degrees of the same process of maldevelopment. The distinguishing feature of the two syndromes, the dextroposition of the aorta, may be difficult to determine owing to the fact that in the absence of the membranous septum there is a physiological overriding of the aorta, and that an examination of the specimen of the heart may not permit an estimate of the degree of dextroposition which existed during life. It is believed, also, that the degree of overriding may be subject to change during a patient's lifetime.

The pathogenesis of cyanosis associated with the Eisenmenger complex is discussed. Evidence is presented that anoxemia and cyanosis are due to admixture of venous blood in the aorta, or the shunt mechanism, rather than to incomplete pulmonary oxygenation.

The hemodynamics of the Eisenmenger complex are presented in the light of recent measurements of intracardiac pressure. Severe pulmonary hypertension has

always been recorded, and in the majority of cases equalization of pressure in the systemic and pulmonary circulation was established. This feature is discussed in connection with the concept of the "double outlet ventricle," in which it is postulated that equal resistance offered by the pulmonary and systemic arterioles is essential for survival and has to be present from birth.

Four cases are included in which the triad of basal defect of the ventricular septum, dextroposition of the aorta and deformity of an aortic cusp causing aortic insufficiency existed. In contrast to the remainder of the series, in three of these cases cyanosis was absent, and in the fourth one it was questionable. It is thought that because of the associated aortic lesion the dextroposition of the aorta was nonfunctioning, and, therefore, it is suggested that these cases be classified as ventricular septal defects and not as Eisenmenger's complex associated with aortic insufficiency.

The Eisenmenger complex is redefined by a combined pathological and physiological set of criteria.

OBSERVATIONS ON A CASE OF IDIOPATHIC HYPOPARATHYROIDISM

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CHRONIC parathyroid insufficiency, in persons who have not had an operation on the thyroid gland, is an exceedingly rare condition. Drake, Albright, Bauer and Castleman,[1] who reported six cases with autopsy observations in one of them, were able to collect from the previous literature only eight other instances which satisfied their diagnostic criteria. They considered that to justify the diagnosis there must be symptoms and signs of chronic tetany, a low serum calcium level, a raised serum inorganic phosphate level, evidence of normal renal function and absence of roentgenologic abnormalities in the bones. The last stipulation, however, requires modification, since increased density of bones has been reported in examples of the syndrome by Sevringhaus [2] and by Taubenhaus and Engle,[3] as well as by Emerson, Walsh and Howard,[4] who stated that Albright, after seeing one of their patients, reexamined the roentgenograms of his own juvenile patients and found the bones to be of increased density in all of them. Other features which may be present include cataracts, epileptiform attacks and defects of hair, teeth, nails and skin.

Since the appearance of the paper by Drake and his colleagues,[1] the diagnosis has been made in at least 20 further patients, but the criteria given above were not always completely fulfilled (Eaton and Haines,[5] three cases; Humphreys [6];

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1. Drake, T. G.; Albright, F.; Bauer, W., and Castleman, B.: Chronic Idiopathic Hypoparathyroidism: Report of Six Cases with Autopsy Findings in One, Ann. Int. Med. **12**:1751, 1939.

2. Sevringhaus, E. L.: Activated Sterols and Calcium Salts in Treatment of Parathyroid Tetany, Am. J. M. Sc. **203**:726, 1942.

3. Taubenhaus, M., and Engle, H. M.: Clinical Observations on a Case of Idiopathic Tetany and Epilepsy, J. Clin. Endocrinol. **5**:147, 1945.

4. Emerson, K., Jr.; Walsh, F. B., and Howard, J. E.: Idiopathic Hypoparathyroidism: A Report of 2 Cases, Ann. Int. Med. **14**:1256, 1941.

5. Eaton, L. M., and Haines, S. F.: Parathyroid Insufficiency with Symmetrical Cerebral Calcification: Report of Three Cases, in One of Which Patient Was Treated with Dihydrotachysterol, J. A. M. A. **113**:749 (Aug. 26) 1939.

6. Humphreys, H. F.: The Teeth from a Case of Hypoparathyroidism, Proc. Roy. Soc. Med. **32**:633, 1939.

Berk[7]; Cantarow, Stewart and Morgan[8]; Franco[9]; Emerson and others,[4] two cases; McQuarrie, Hansen and Ziegler[10]; Kowallis[11]; Sevringhaus[2]; Cantor and Scott[12]; Sutphin, Albright and McCune,[13] five cases; Taubenhaus and Engle[3]; Mortell[14]). Lachmann[15] has published a monograph on hypoparathyroidism in Denmark, in which he included 22 examples of the idiopathic variety; a review of the protocols, however, makes it clear that the criteria were by no means strict and in many cases the diagnosis must be regarded as doubtful. Patients have also been described in whom chronic parathyroid insufficiency was associated with chronic hypothyroidism (Himsworth and Maizels[16]), with Addison's disease (Leonard[17]) and with cerebral trauma (Winer[18]). Albright, Burnett, Smith and Parson[19] described three instances of "pseudohypoparathyroidism," a condition clinically resembling idiopathic hypoparathyroidism but due, in their opinion, to failure of response to the normal parathyroid secretion rather than to primary insufficiency of the parathyroid glands; a similar case has since been published by Sprague, Haines and Power.[20]

We have had the opportunity of studying a patient displaying most of the phenomena which may be associated with idiopathic hypoparathyroidism.

REPORT OF CASE

R. E., a boy 17 years of age employed in a brewery, was admitted to the Royal Hospital, Sheffield, on Nov. 20, 1947 under the care of one of us (A. R. K.).

7. Berk, J. E.: Clinical Experience with Dihydrotachysterol in the Management of Idiopathic Hypocalcemia: Report of a Case, Endocrinology **25**:984, 1939.

8. Cantarow, A.; Stewart, H. L., and Morgan, D. R.: Chronic Idiopathic Parathyroid Tetany, Endocrinology **24**:556, 1939. This case is apparently the same as one reported earlier (Cantarow, A.: Chronic Juvenile Hypoparathyroidism, Arch. Pediat. **49**:293, 1932) and included in the review by Drake and his co-workers.[1]

9. Franco, S. C.: Parathyroid Tetany: Chronic Idiopathic Parathyroid Insufficiency of 10 Years' Duration Successfully Controlled with Dihydrotachysterol, Ann. Int. Med. **14**:529, 1940.

10. McQuarrie, I.; Hansen, A. E., and Ziegler, M. R.: Studies on the Convulsive Mechanism in Idiopathic Hypoparathyroidism, J. Clin. Endocrinol. **1**:789, 1941.

11. Kowallis, G. F.: Spontaneous Parathyroid Insufficiency: Report of a Case, Proc. Staff Meet., Mayo Clin. **16**:129, 1941.

12. Cantor, M. M., and Scott, J. W.: Chronic Idiopathic Hypoparathyroidism, Canad. M. A. J. **47**:551, 1942.

13. Sutphin, A.; Albright, F., and McCune, D. J.: Five Cases (3 Siblings) of Idiopathic Hypoparathyroidism Associated with Moniliasis, J. Clin. Endocrinol. **3**:625, 1943.

14. Mortell, E. J.: Idiopathic Hypoparathyroidism with Mental Deterioration: Effect of Treatment on Intellectual Function, J. Clin. Endocrinol. **6**:266, 1946.

15. Lachmann, A.: Hypoparathyroidism in Denmark: A Clinical Study, Acta med. Scandinav., 1941, supp. 121, p. 1.

16. Himsworth, H. P., and Maizels, M.: Vitamins D_2 and D_3 and A.T. 10 in Congenital Thyroid and Parathyroid Deficiency, Lancet **1**:959, 1940.

17. Leonard, M. F.: Chronic Idiopathic Hypoparathyroidism with Superimposed Addison's Disease in a Child, J. Clin. Endocrinol. **6**:493, 1946.

18. Winer, N. J.: Hypoparathyroidism of Probable Encephalopathic Origin, J. Clin. Endocrinol. **5**:86, 1945.

19. Albright, F.; Burnett, C. H.; Smith, P. H., and Parson, W.: Pseudo-Hypoparathyroidism—An Example of "Seabright-Bantam Syndrome": Report of 3 Cases, Endocrinology **30**:922, 1942.

20. Sprague, R. G.; Haines, S. F., and Power, M. H.: Metabolic Effects of Parathyroid Hormone, Dihydrotachysterol, and Calciferol in a Case of Pseudohypoparathyroidism, J. Lab. & Clin. Med. **30**:363, 1945.

The patient complained of muscular twitchings and of attacks of "dizziness." Apart from measles, mumps and chickenpox in early childhood, he was well until the age of 9 years, when he had an appendectomy for acute appendicitis; he was then noticed to be small for his age. At that time he began to suffer from frequent muscular twitchings, involving chiefly the muscles of the face and arms, the sternocleidomastoids and the pectorals; these twitchings had persisted to the time of his admission. Details could not be obtained regarding his deciduous teeth, but he recollected removing some himself, and others were removed between the ages of 10 and 12 by a dentist.

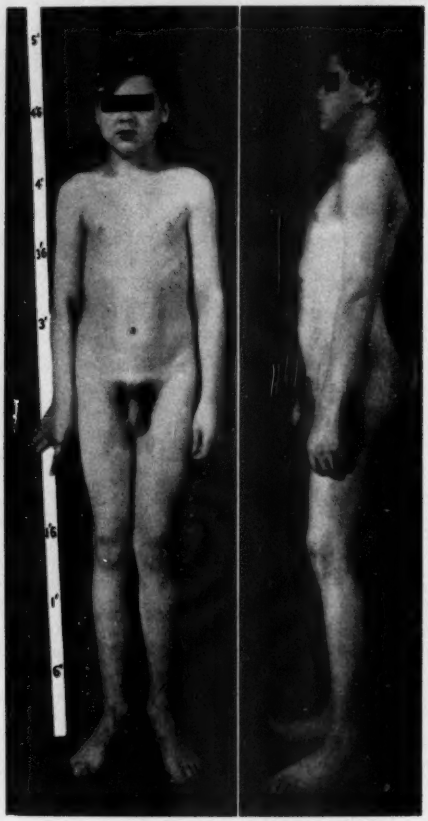

Fig. 1.—Front and side views of patient R. E. The ruler alongside is marked in feet and inches.

At the age of 15½ years he began to have "attacks." The first of these consisted of a feeling of dizziness, with blurring of vision, followed by loss of consciousness for about half a minute; he thought that he bit his tongue, but he did not soil himself, and after regaining consciousness he was left with a slight headache. Later attacks, of which there were four or five during the 12 months before admission, consisted of a feeling of dizziness with counterclockwise rotation of objects; the right foot seemed to "screw inward," and a tingling feeling passed up his right leg toward his head. The whole body "went stiff," and if he gripped

anything relaxation proved difficult and the hands tended to assume the *accoucheur* position. These attacks lasted about half a minute and were not accompanied with loss of consciousness.

For three years he had suffered from frequent occipital headaches. There had been no urinary symptoms other than occasional "stinging." His appetite was excellent; his diet had always been normal, and no abnormality of the stools had ever been noted. He had not yet shaved and apparently never had nocturnal emissions; he "did not bother with girls." Since he was 9 years old he had always been undersized for his age.

Family History.—Both his parents were alive and well. He had one brother, aged 12, who had chorea, and one sister, aged 7, who was well. No member of the family had any symptoms suggesting parathyroid disease.

Condition on Admission.—The patient was found to be a short, sturdy boy (height, 4 feet 9 inches [145 cm.]; weight, 85 pounds [39 Kg.]), mentally alert and cooperative. His voice

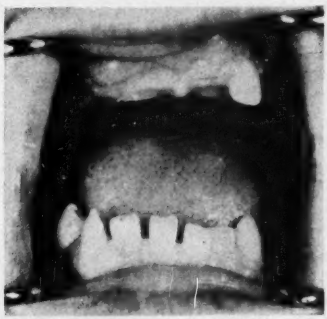

Fig. 2.—Erupted teeth of R. E.

Fig. 3.—Lower first right molar tooth of R. E., showing pitting of enamel.

was of normal pitch for his age and sex. He was afebrile and remained so throughout his stay in hospital. Scalp hair was abundant and in good condition, and the eyebrows were full. There was a small growth of hair on the upper lip, but none in the beard area. Axillary hair was scanty; pubic hair was abundant, but the contour of the upper border was of feminine type (fig. 1). There were frequent involuntary coarse muscular twitchings, involving the face, arms and trunk, and Chvostek's sign was easily elicited on both sides. The mucous membranes were well colored. Small nodes were palpable on both sides of the neck and in the axillas, but there was no enlargement of inguinal or epitrochlear nodes. The only erupted teeth were the upper second left incisor, the lower incisors and canines, the lower first right premolar and the lower first right molar; palpation of the gums suggested the presence of many unerupted teeth. The erupted teeth showed some notching, with pitting of the enamel (figs. 2 and 3). All the finger nails showed small white spots but were otherwise normal.

No abnormality was found on examination of the heart, lungs or abdomen. The blood pressure was 115/70 mm. of mercury. The genitalia were well developed. Complete neurological examination disclosed no abnormality. The urine was of normal appearance, and tests for albumin and sugar gave negative reactions.

Examination of the eyes by Mr. W. Ingman, First Assistant to the Ophthalmic Department, revealed no cataract or other abnormality at this time.

Initial Investigations.—1. Trousseau's Phenomenon: On one occasion occlusion of the circulation to the right arm by a sphygmomanometer cuff inflated to a pressure of 180 mm. of mercury produced the typical *main d'accoucheur* after two minutes; the occlusion was continued, and four minutes from the start the hand had again become flaccid. Subsequent attempts to elicit this sign were unsuccessful.

2. Effect of Voluntary Hyperpnea: The circulation to the left arm was occluded by a sphygmomanometer cuff, and overbreathing was begun. After seven minutes, there was a noticeable increase in muscular twitching in the legs, with dorsiflexion of the big toes. Ten minutes after the start the right hand was in well marked spasm in the *main d'accoucheur* position, but the left hand was still flaccid. At 11 minutes the circulation to the left arm was released, overbreathing being continued, and the left hand went into definite spasm in the *main d'accoucheur* position 1½ minutes later.

3. Blood Examinations: The hemoglobin concentration was 14.9 Gm. per 100 ml. Red blood cells numbered 5,020,000 and white blood cells 6,000, with 4,020 (67 per cent) polymorphonuclear leukocytes, 1,800 (30 per cent) lymphocytes, 120 (2 per cent) monocytes and 60 (1 per cent) basophils, per cubic millimeter. The sedimentation rate was 10 mm. in one hour (Westergren method, using a 200 mm. column).

Serum calcium was 6.3 mg. and serum inorganic phosphate (as phosphorus) 9.1 mg. per 100 ml. Serum alkaline phosphatase measured 33 King-Armstrong units. Serum magnesium was 3.7 mg. and blood urea 38 mg. per 100 ml.; the alkali reserve was 74 ml. of carbon dioxide per 100 ml. of plasma. Total serum protein measured 6.9 Gm., with 4.3 Gm. of serum albumin and 2.6 Gm. of serum globulin (by difference) per 100 ml. The serum calcium, serum inorganic phosphate, serum alkaline phosphatase, blood urea and alkali reserve were determined as described by Harrison,[21] and serum magnesium levels as described by Garner.[22] Serum protein and albumin were determined by the micro-Kjeldahl method, the globulin being precipitated by 22.5 per cent sodium sulfate solution at 37 C. (calculation: 1 mg. of nitrogen is equivalent to 6.25 mg. of protein, with no correction for nonprotein nitrogen). The Wassermann reaction was negative.

4. Urea Clearance Test (Van Slyke): In the first hour the maximum clearance was 104 per cent of average normal, and the second hour the standard clearance was 70 per cent of average normal.

5. Electrocardiogram: The QRS complex was of low voltage in lead III and the T wave in lead III was inverted. The Q-T interval was 0.36 second, the heart rate being 94 per minute; the extreme upper limit of normality for the Q-T interval at this heart rate, according to the formula of Hegglin and Holzmann,[23] is 0.35 second.

6. Roentgenologic Examination (Drs. T. Lodge and R. Steiner): No roentgenologic abnormality was seen in films of the chest and abdomen. Roentgenograms of the skull showed bilateral mottled calcification in the frontal areas, arranged in cylindrical fashion along the line of the lateral ventricles (figs. 4 and 5); it was thought that this calcification might be associated with the choroid plexus. Roentgenograms of the limbs showed some delay in ossification and some sclerosis of the distal ends of the diaphyses of the long bones. There was no evidence of vascular calcification. Roentgenograms of the jaws showed numerous unerupted

21. Harrison, G. A.: Chemical Methods in Clinical Medicine, ed. 3, London, J. & A. Churchill, Ltd., 1947.

22. Garner, R. J.: Colorimetric Determination of Magnesium in Plasma or Serum by Means of Titan Yellow, Biochem. J. **40**:828, 1946.

23. Hegglin, R., and Holzmann, M.: Die klinische Bedeutung der verlängerten QT-Distanz (Systolendauer) im Elektrokardiogramm, Ztschr. f. klin. Med. **132**:1, 1937.

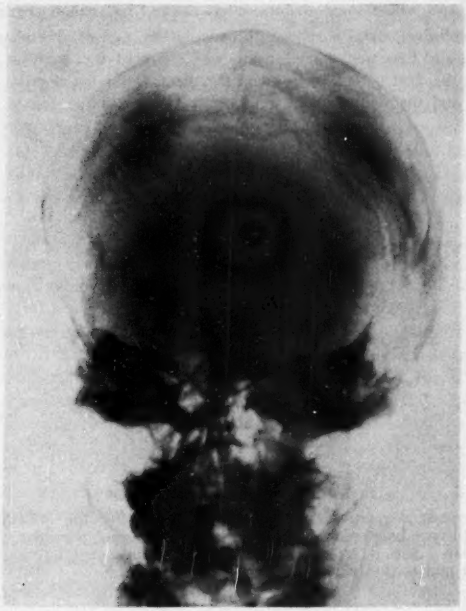

Fig. 4.—Posteroanterior roentgenogram of skull of R. E., showing bilateral cerebral calcification.

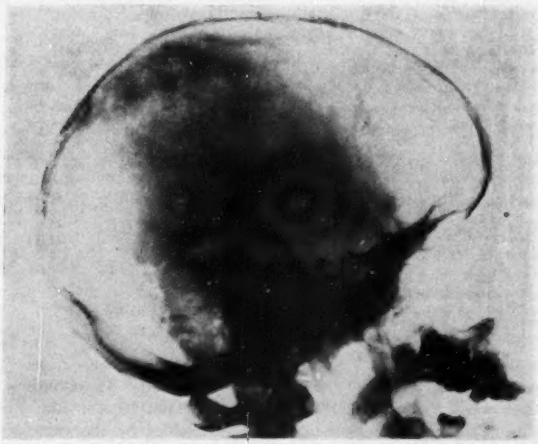

Fig. 5.—Lateral roentgenogram of skull of R. E., showing cerebral calcification.

teeth in both upper and lower jaws, some lying at extraordinary angles. Subsequent roentgenograms of the jaws, taken seven months later, showed no change (fig. 6).

7. Calcium, Magnesium and Phosphorus Balance: The patient was placed on a fixed diet, identical each day, for two weeks. All urine was collected for analysis over two separate three day periods; the first period accustomed the members of the nursing staff to the collection of specimens, and the findings served to confirm those in the second. Carmine markers

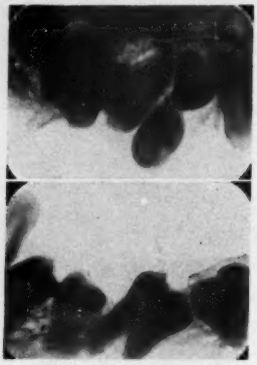

Fig. 6.—Top, roentgenogram of right upper jaw, showing the following unerupted teeth of the second dentition: lateral incisor, canine, first and second premolar, first molar and part of the second molar. Bottom, roentgenogram showing unerupted left lower first and second premolar and first and second permanent molar teeth of R. E.

TABLE 1.—*First Calcium, Phosphorus and Magnesium Balance Study*

	Calcium, Mg.	Phosphorus, Mg.	Magnesium, Mg.
Diet			
Analysis of 1st duplicate (1 day)	1,008	1,408	222
Analysis of 2d duplicate (1 day)	938	1,427	102
Average diet for 1 day *	1,003	1,418	162
Food not eaten during test period	197	502	72
Urine			
1st 3 day period	42	2,615	Less than 15
Test period (3 days)	18	2,606	Less than 15
Feces			
Test period (3 days)	2,710	2,170	318
Balance			
Food eaten †	2,812	3,752	414
Total excretion ‡	2,728	4,778	333
Balance (3 days)	+84	—1,026	+81
Balance, average for 1 day	+28	—342	+27

* Mean of first and second duplicates.
† Three times "Average diet for 1 day" less "Food not eaten during test period."
‡ Urine for test period plus feces for test period.

were given at the beginning and end of the second three day period, and all stools were collected between the first appearance and the reappearance of the carmine. Two duplicates of the daily diet were analyzed, and the balance was worked out from the mean of the analytical results. Calcium and magnesium were determined by the methods of McCrudden (see Hawk and Bergeim [24]), and phosphorus was determined as described by McCance and

24. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, ed. 11, London J. & A. Churchill, Ltd., 1938, pp. 772-773.

Shipp.[25] The patient was found to be retaining a small quantity of calcium and magnesium but to be losing an appreciable amount of phosphorus (table 1); it is doubtful whether the retention of calcium and magnesium is large enough to be significant.

Progress, Subsequent Investigations and Treatment.—During the period of initial observation and investigation, which lasted four weeks, the patient continued to have frequent muscular twitching, a strongly positive Chvostek sign and recurrent attacks of severe muscular spasm, chiefly affecting the right leg. These attacks were not associated with loss of consciousness, but the patient found them alarming and distressing, and he was, therefore, given phenobarbital, ½ grain (0.03 Gm.) twice daily, from November 29 onward; this did not diminish the incidence of the attacks, but the patient seemed to be less worried by them than previously.

On December 19, the serum calcium was 7.1 mg. and the serum inorganic phosphate (as phosphorus) was 7.1 mg. per 100 ml. On this date treatment was begun with calcium lactate, 12 Gm. daily by mouth (equivalent to about 1.56 Gm. of calcium); this was continued until Jan. 18, 1948 (30 days), but no sustained change occurred in the serum calcium or serum inorganic phosphate levels (see fig. 7), and on January 15 the serum alkaline phosphatase was still raised (25 units). After a break of 11 days, during which the serum calcium fell slightly, calcium lactate was again given in the same dosage (12 Gm. daily), combined with calciferol U. S. P., 30,000 international units daily (given as high potency ostelin® tablets). Twelve days later (February 10), the dosage of calcium lactate was increased to 16 Gm. daily (equivalent to about 2.08 Gm. of calcium) and the dosage of calciferol was raised to 50,000 international units daily. The dose of calciferol was adopted in view of the report of Anderson and Lyall[26] that in cases of postoperative hypoparathyroidism the minimal dose of vitamin D required to raise the serum calcium to normal appeared to be 30,000 to 45,000 international units daily. On February 18, the serum calcium was still only 7.0 mg. and the serum inorganic phosphate had reached the high figure of 10.1 mg. per 100 ml.

At this stage we became aware of the paper by Albright, Burnett, Smith and Parson[19] on pseudohypoparathyroidism; the three cases reported by them presented clinical and biochemical findings resembling those in idiopathic hypoparathyroidism, but the condition was resistant to treatment with parathyroid extract and somewhat resistant to dihydrotachysterol (A.T. 10) therapy. All three patients were of similar appearance with round faces and thickset figures; our patient showed the same physical features, and, in consequence, we attempted to discover whether he reacted normally to injected parathyroid extract. Treatment with calcium lactate and calciferol was suspended, and three days later the test was begun. The urine was collected for three successive 24 hour periods; the patient was given an intramuscular injection of 200 units of parathyroid extract (parathormone®), and then the urine was collected for a further three successive 24 hour periods. Each 24 hour specimen of urine was analyzed for calcium, phosphorus and magnesium by the methods employed for the balance experiments. The serum calcium, serum inorganic phosphate and serum magnesium were determined immediately before the injection and 8, 12 and 24 hours after. The results are shown in table 2; we concluded from the rise in serum calcium and the fall in serum inorganic phosphate that the patient was capable of responding to injected parathyroid extract. The increase in urinary calcium and phosphorus is consistent with this, but statistical examination (Student's t test) shows that the increases in urinary calcium and urinary phosphorus could arise by chance eight times in 100 and three times in 10, respectively. The necessity for observations on a control patient in this type of experiment was emphasized by the fact that the first preparation of parathyroid extract which we tried proved to be quite inert, though marketed by a well known firm.

Treatment with calcium lactate, 16 Gm. daily, and calciferol, 50,000 international units daily, was resumed after the completion of this experiment (February 27), and after 10 days the

25. McCance, R. A., and Shipp, H. L.: The Chemistry of Flesh Foods and Their Losses on Cooking, Special Report Series 187, London, Medical Research Council, 1933.

26. Anderson, I. A., and Lyall, A.: The Treatment of Chronic Hypoparathyroidism, Quart. J. Med. **8**:209, 1939.

dose of calciferol was raised to 100,000 international units daily and 29 days later to 150,000 international units. However, 60 days after resumption of this treatment (April 27) the serum calcium was still only 7.5 mg. and the serum inorganic phosphate (as phosphorus) 7.2 mg.

TABLE 2.—*Results of Intramuscular Injection of 200 Units of Parathyroid Extract*

	Serum (Patient and Control)				
	Patient			Control	
	Serum Calcium, Mg./100 Ml.	Serum Inorganic Phosphorus, Mg./100 Ml.	Serum Magnesium, Mg./100 Ml.	Serum Calcium, Mg./100 Ml.	Serum Inorganic Phosphorus, Mg./100 Ml.
Immediately before injection	6.2	8.0	2.4	10.2	4.9
8 hr. after injection	7.9	7.0	2.6	11.1	3.8
12 hr. after injection	7.4	8.0	2.3	11.0	4.7
24 hr. after injection	7.0	7.7	2.4	11.3	4.8

	Urine (Patient Only)		
	Calcium (24 Hr. Excretion), Mg.	Phosphorus (24 Hr. Excretion), Mg.	Magnesium (24 Hr. Excretion), Mg.
72 to 48 hr. before injection	3	1,080	157
48 to 24 hr. before injection	3	890	124
24 to 0 hr. before injection	4	980	112
0 to 24 hr. after injection	5	1,000	118
24 to 48 hr. after injection	10	1,050	151
48 to 72 hr. after injection	11	1,550	100

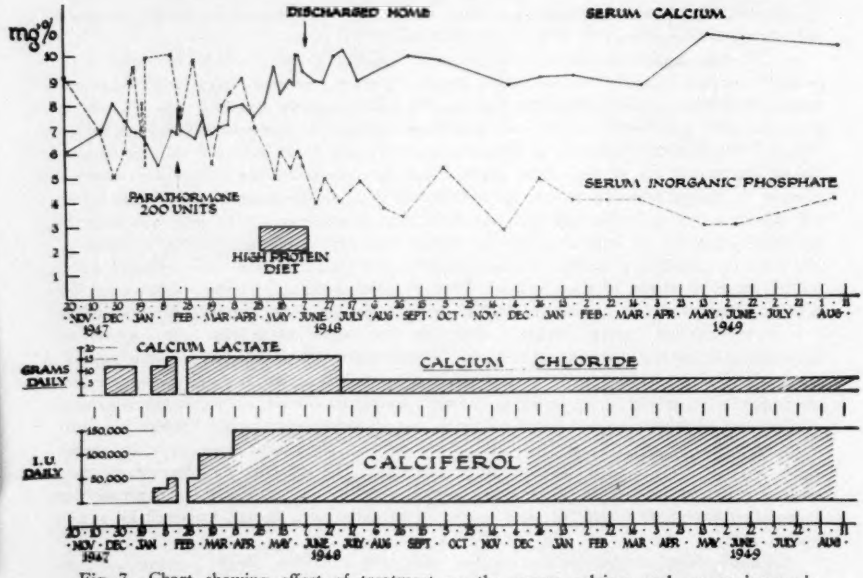

Fig. 7.—Chart showing effect of treatment on the serum calcium and serum inorganic phosphate levels of R. E. The serum inorganic phosphate is expressed as milligrams of phosphorus per 100 ml. of serum.

per 100 ml., neither having shown any conspicuous change, although there had been a slow rise in the serum calcium level (see fig. 7). The serum alkaline phosphatase remained elevated, values of 20 to 32 units being found between March 22 and April 27.

So far the patient had been eating an ordinary ward diet except during the balance experiments. A low phosphorus diet, the beneficial effects of which were demonstrated in postoperative hypoparathyroidism by Anderson and Lyall,[28] had been dismissed as impracticable in present circumstances in Great Britain, since the foodstuffs of which the consumption would need to be limited were essentially those which contribute most of the protein (meat, fish, milk, cheese, eggs). At this point, we became aware of the papers of McCance, Widdowson and Lehmann [27] and Hall and Lehmann,[28] which suggested that calcium absorption could be increased by raising the intake of protein. It was decided to try the effect of a high protein diet (approximately 130 Gm. of protein daily), and this was begun on May 1, the daily dosage of calcium lactate and calciferol remaining unchanged (16 Gm. and 150,000 international units, respectively). The result was striking; a somewhat irregular but notable rise in the serum calcium and a fall in the serum inorganic phosphate occurred (see fig. 7). After 32 days on the high protein diet, the serum calcium was 10.1 mg. and the serum inorganic phosphate (as phosphorus) 6.1 mg. per 100 ml. The serum alkaline phosphatase remained substantially unchanged; it varied between 21 and 34 units during the period May 7 to June 7. As the serum calcium rose to normal levels, the muscular twitchings diminished and finally disappeared; Chvostek's sign

TABLE 3.—*Second Calcium and Phosphorus Balance Study and Fat Balance Study*

	Calcium, Mg.	Phosphorus, Mg.	Fat, Gm.
Diet			
Analysis of 1st duplicate (1 day)	2,016	3,080	85
Analysis of 2d duplicate (1 day)	2,018	2,985	91
Average diet for 1 day *	2,017	3,032	88
Calcium lactate powders (1 day)	2,020	.....	..
Urine			
Test period (5 days)	19	11,900	..
Feces			
Test period (5 days)	16,500	5,230	26
Balance			
Food (5 days) †	10,085	15,160	440
Calcium lactate (5 days) ‡	10,100	.....	..
Total intake	20,185	15,160	440
Total excretion §	16,519	17,220	26
Balance (5 days)	+3,666	—2,060	+414
Balance, average for 1 day	+733	—412	+83

* Mean of first and second duplicates.
† Five times "Average diet for 1 day."
‡ Five times "Calcium lactate powders (1 day)."
§ Urine for test period plus feces for test period.

became negative, and the major attacks of tetany ceased. The administration of phenobarbital was stopped on May 13.

In view of the unequivocal changes in the serum calcium and the serum inorganic phosphate, which we believe to be attributable to the high protein diet, a second balance experiment was carried out while the patient was still receiving this diet. The opportunity was taken to determine the fat balance at the same time to exclude the possibility that the clinical picture and biochemical changes might be due to chronic steatorrhea, in spite of the normal macroscopic appearance of the stools. The experiment was carried out over a five day period, from May 31 to June 5. Two days before the collection of specimens began the patient was placed on a fixed high protein diet, identical each day; administration of calcium lactate, 16 Gm. daily, and calciferol, 150,000 international units daily, was continued throughout, duplicate samples of the calcium lactate powders being sent to the laboratory for analysis. Beginning on May 31, five successive 24 hour collections of urine were made, and all feces were collected between

27. McCance, R. A.; Widdowson, E. M., and Lehmann, H.: The Effect of Protein Intake on the Absorption of Calcium and Magnesium, Biochem. J. **36**:686, 1942.

28. Hall, T. C., and Lehmann, H.: Experiments on the Practicability of Increasing Calcium Absorption with Protein Derivatives, Biochem. J. **38**:117, 1944.

the appearances of carmine markers given on May 31 and June 5, respectively. Two duplicates of the daily diet were analyzed, and the balance was calculated from the mean figures. The methods of analysis for calcium and phosphorus were identical with those employed for the first balance study. Fat was estimated by extracting the dried foodstuffs with ether in the Soxhlet apparatus and weighing the fat after evaporation of the solvent. Feces were mixed to dryness with anhydrous sodium sulfate before being extracted. The results are shown in table 3. On the average, 733 mg. of calcium was being retained daily, as compared with 28 mg. shortly after admission to hospital. The daily average loss of phosphorus was 412 mg., as compared with 342 mg. in the first balance experiment. Ninety-four per cent of the ingested fat was absorbed. The possible significance of the results of the calcium and phosphorus balance experiments will be discussed later; the results of the fat balance study exclude steatorrhea.

The patient was discharged from the hospital on June 10 with instructions to eat a normal diet and to continue to take calcium lactate, 16 Gm. daily, and calciferol, 150,000 international units daily. He has since been followed as an outpatient. He found the calcium lactate awkward to take at home, and so on July 9 it was changed to calcium chloride, 6 Gm. daily, in a mixture; it was estimated that this amount would provide approximately the same quantity of calcium (about 2 Gm.) as the previous dosage of calcium lactate. The patient found the solution preferable to the powder. Since discharge from hospital he has remained free from symptoms and signs of tetany and has returned to work. The serum calcium has varied between 8.8 and 10.9 mg. and the serum inorganic phosphate (as phosphorus) between 5.4 and 2.8 mg. per 100 ml.; the alkaline phosphatase has tended to fall (20 units on June 188, 1948; 14 units on June 10, 1949; 16 units on Aug. 5, 1949). During the period June 22, 1948 to Aug. 5, 1949, the calcium contents of seven midmorning specimens of urine have varied between 0.4 and 8.5 mg. per 100 ml. of urine; on the whole, the later figures have tended to be the higher. Since his discharge from the hospital, a study with a histamine test meal has been done, which showed good secretion of hydrochloric acid.

Two further examinations were carried out by Mr. Ingman, who reported as follows:

June 21, 1948: I have found some lenticular changes this time. There are in both eyes several opacities, cortical in distribution though not confined to any particular level. These opacities are in the form of streaks and also in flecks. They have sharply defined edges. I would say they are the particular opacities that one would find in this type of case. The opacities do not seem to affect the patient's vision.

Aug. 5, 1949: The opacities previously noted are much less dense and do not appear to be so numerous. They are now rather difficult to see, except at the periphery. This is not, in my opinion, because of their greater depth, although they are now situated in a deeper cortical zone covered by a clear zone; I think that they themselves are less opaque. The lens fibers since laid down are transparent. The appearances on slit lamp examination would suggest that the cataractous changes noted at the second examination (on June 21, 1948) have regressed and that the fibers laid down since then have not been exposed to the same conditions as those which had previously operated.

Mr. Ingram's report continued:

Several authors (Jacques [29]; Cole [30]; O'Brien [31]) stated that treatment of the tetany accompanying postoperative hypoparathyroidism has little effect on the development of cataract, which tends to progress even though the general symptoms are controlled. Reference to their papers, however, showed that the treatment given was inadequate by modern standards, in that the serum calcium was not raised to normal in any patient for more than brief periods. The appearances noted in this patient's lenses would suggest that, provided the treatment is sufficient to maintain a normal calcium level, the cataractous changes may not progress. There seems no reason why this should not be true of postoperative cases as of this case of idiopathic hypoparathyroidism.

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29. Jacques, L.: Cataract and Post-Operative Tetany, Am. J. M. Sc. **175**:185, 1928.

30. Cole, L.: Parathyroid Tetany and Cataract, Lancet **1**:13, 1930.

31. O'Brien, C. S.: The Cataract of Postoperative Tetany, with a Report of 3 Cases, Arch. Ophth. **7**:71 (Jan.) 1932.

A special dental examination was made by Mr. J. J. Hodson, Dental Pathologist, University of Sheffield, who reported as follows (Aug. 16, 1948):

The following teeth were erupted: $\frac{6\ 4\ 3\ 2\ 1}{1\ 2\ 3}\ \frac{2}{1}\ \frac{4\ 2}{\ }\ \frac{4}{\ }$ are in the process of erupting. $\frac{\ }{6\ 1}\ \frac{\ }{1}$ show hypoplastic defects in the position which suggests some disturbance to amelogenesis between the ages of 1 and 2. The erupted teeth appear translucent and of normal calcification. The lower incisors show a number of pulp stones. The unerupted teeth which make up the full complement are situated in a bizarre fashion, overcrowded and in various degrees of impaction. The upper central and the three first permanent molars show roentgenographically the same hypoplastic defects as those mentioned above and give the same age position. The alveolus appears to be within the range of normal. The gingivae are firm and well keratinized, with no calculous deposits. The oral condition in this case presents features similar to those described in the literature, especially the retarded eruptions, the bizarre position of the dentition and the hypoplastic defects. The particular hypoplastic defects in this case are as typical of rickets and defective amelogenesis in the course of the exanthematous fevers as they are of tetany. The onset of his present symptoms at about 9 years of age does not coincide with the age at which his enamel defects occurred. It may be that the child had mild tetany at a much earlier age. The presence of pulp stones is a fairly common occurrence in normal mouths, but in this patient one wonders whether they have appeared since his calcium intake was increased.

Mr. Hodson carried out a further examination on Aug. 5, 1949 and reported as follows:

There is little change in this boy's oral condition. Roentgenograms show some slight progression of eruption of one or two of the unerupted teeth. $\frac{4}{\ }$ has moved forward in eruption but is not through the gum yet. The buccal cusp of $\frac{4}{\ }$ has erupted, and $\frac{2\ 1}{\ }\ \frac{1}{\ }$ seem to be erupting in the labial sulcus but are not through the gum yet. Since the earlier examination there has been no apparent increase in size or number of the pulp stones. There is some indication of a slight deterioration in oral hygiene. A little calculus is present on the lower incisors. The latter is not considered relevant to his general condition, but, as no salivary calcium estimation was done, it is not known whether this slight deposit is due to any increased salivary calcium.

Roentgenograms of the skull taken on Aug. 5, 1949 showed no changes in the intracerebral calcification. Roentgenograms of the trunk and limbs revealed no evidence of calcification in blood vessels or in the renal tract.

COMMENT

Diagnosis.—We feel that there can be no doubt of the diagnosis of idiopathic hypoparathyroidism in this case. Chronic tetany, a persistently low serum calcium and a persistently high serum inorganic phosphate in a boy whose renal function and fat absorption are normal, whose diet has always been good, who has never been subjected to any operation on the neck and who responds to an injection of parathyroid extract constitute a combination of features which scarcely allows an alternative diagnosis.

Etiological Aspects.—The causation of the condition can be only a matter for conjecture, since autopsy records of cases of idiopathic hypoparathyroidism are very few. Drake and his co-workers [1] reported one case, that of a boy observed from the age of 5 years until his death at 13 years, in whom the parenchyma of the parathyroid glands was entirely replaced by fat cells. Cantarow and associates [8] performed an autopsy on a girl studied from the age of 6 years until her death at 12 years, in whom a thorough search failed to reveal any trace of parathyroid tissue. Leonard [17] described associated hypoparathyroidism and Addison's disease in a girl who was observed from the age of 9½ years until her death 2½ years

later, in whom no parathyroid glands could be found at autopsy and the cortex of the adrenal glands was replaced by connective tissue. Thus, it appears that in cases of hypoparathyroidism the parathyroid glands may be either absent or replaced by nonglandular tissue. We did not consider surgical exploration of the parathyroid glands to be justifiable in our case.

Clinical Features of Special Interest.—There are certain clinical features presented by this case or reported in the literature to which we feel that special attention may usefully be directed; they comprise neurological and ectodermal manifestations.

Neurological Manifestations; Epilepsy: The first major attack which our patient experienced had many features suggestive of epilepsy, and the way in which subsequent attacks of tetany invariably started in the right foot was reminiscent of epilepsy of the jacksonian type. The association of chronic tetany with epilepsy has frequently been described in idiopathic hypoparathyroidism by Barr, MacBryde and Sanders,[32] Eaton and Haines,[5] Drake and his co-workers,[1] Himsworth and Maizels,[16] Franco,[9] McQuarrie and his colleagues,[10] Kowallis,[11] Sutphin and associates,[13] Taubenhaus and Engle [3] and Mortell [14]; in postoperative tetany by Barr and others,[32] Odoriz, del Castillo, Manfredi and de la Balze [33] and Levy,[34] and in pseudohypoparathyroidism by Albright and his co-authors.[19] A mistaken diagnosis of idiopathic epilepsy has occasionally been made in cases of chronic tetany due to hypoparathyroidism (Franco [9]; Albright and others [19]; Levy [34]). Abnormal electroencephalographic tracings have been recorded in cases of parathyroid insufficiency (Kowallis [11]; Sutphin and others [13]; Odoriz and others [33]), and improvement in both the epilepsy and the electroencephalographic pattern has been reported after correction of the hypocalcemia by appropriate treatment (Taubenhaus and Engle [3]; Mortell [14]). The reason for the association of epilepsy with chronic hypocalcemic tetany is not known; a low serum calcium is one of the many factors which may precipitate seizures in potential epileptics, and Taubenhaus and Engle [3] believed that the association is purely coincidental.

Mental Changes: In hypoparathyroidism, both idiopathic (Emerson and others [4]; Mortell [14]) and postoperative (Scarlett and Houghtling [35]), profound mental disturbances and even psychoses may occur apart from epilepsy. Improvement in the mental condition may follow the correction of the hypocalcemia.

Papilledema: This is a rare neurological complication of chronic tetany. Albrecht [36] drew attention to the association and cited 10 previous references; since then it has been recorded in cases of both idiopathic hypoparathyroidism (Barr and others [32]; Sutphin and others [13]) and chronic postoperative tetany (Barr and

32. Barr, D. P.; MacBryde, C. M., and Sanders, T. E.: Tetany with Increased Intracranial Pressure and Papilledema: Results from Treatment with Dihydrotachysterol, Tr. A. Am. Physicians **53**:227, 1938.

33. Odoriz, J. B.; del Castillo, E. B.; Manfredi, J. F., and de la Balze, F. A.: Parathyroid Insufficiency and the Human Electroencephalogram, J. Clin. Endocrinol. **4**:493, 1944.

34. Levy, H. A.: Unusual Clinical Manifestations of Chronic Hypoparathyroidism, M. Clin. North America **31**:243, 1947.

35. Scarlett, E. P., and Houghtling, W. J.: Psychosis in Hypoparathyroidism, Canad. M. A. J. **50**:351, 1944.

36. Albrecht, K.: Stauungspapille bei Tetanie, Monatsschr. f. Psychiat. u. Neurol. **55**:55, 1923.

others [32]; Levy [34]). The mechanism is obscure; the pressure of the cerebrospinal fluid is raised in such cases (Albrecht [36]; Barr and others [32]; Sutphin and others [13]; Levy [34]), but the calcium content (total and ionic) was normal in the only case in which it appears to have been estimated (Barr and others [32]).

Intracerebral Calcification: The occurrence of symmetrical cerebral calcification was described in three cases of idiopathic hypoparathyroidism by Eaton and Haines,[5] who also cited from the German literature records of seven cases in which autopsies had been performed. The calcification is usually in the region of the basal ganglions but may be in the choroid plexus, as is probably the case in our patient. According to Eaton and Haines,[5] the underlying pathological change is one of colloid deposition, with subsequent calcification in and around the finer cerebral blood vessels, and they stated that a similar change may occur in other diseases. Intracerebral calcification, demonstrable roentgenologically, has been recorded in other cases of idiopathic hypoparathyroidism (Drake and others [1]; Sevringhaus [2]; Mortell [14]; Leonard [17]) and in a case of pseudohypoparathyroidism (Sprague and others [20]).

Ectodermal Lesions: The association of cataract with chronic tetany is well known and has been described in most of the recorded cases of idiopathic hypoparathyroidism. Dryness and scaliness of the skin, brittleness of the nails and loss of hair have been reported in several cases (Berk [7]; Cantarow and others [8]; Emerson and others [4]; Cantor and Scott [12]), and Sutphin and his co-workers [13] have described five cases associated with chronic monilial infection of the mouth or nails. The association of skin disease and chronic tetany has been exhaustively reviewed by Lachmann.[15]

Dental abnormalities may also occur, particularly when the onset is in childhood. Defective formation of enamel and dentine is found in the incisors of parathyroidectomized rats with long survival periods (Schour, Chandler and Tweedy,[37] who gave many other references), and similar changes may occur in idiopathic hypoparathyroidism in man (Humphreys [6]). Retarded eruption of teeth, as in our patient, does not appear to be such a well recognized phenomenon but has been described in idiopathic hypoparathyroidism (Emerson and others [4]; Mortell [14]) and in pseudohypoparathyroidism (Albright and others [19]).

Biochemical Findings.—Low serum calcium and high serum inorganic phosphate levels, with low urinary excretion of calcium, are essential features of idiopathic hypoparathyroidism. It has been suggested that there is a "threshold" for serum calcium at a level of about 8.5 mg. per 100 ml., below which urinary excretion of calcium is constant but above which urinary calcium varies with the serum calcium level (Albright and Ellsworth [38]), and this has been made the basis of a scheme for controlling therapy in cases of chronic hypocalcemic tetany by roughly estimating the urinary calcium with the Sulkowitch reagent (Albright [39]). It is worthy of

37. Schour, I.; Chandler, S. B., and Tweedy, W. R.: Changes in the Teeth Following Parathyroidectomy, Am. J. Path. **13**:945 and 971, 1937.

38. Albright, F., and Ellsworth, R.: Studies on the Physiology of the Parathyroid Glands: I. Calcium and Phosphorus Studies on a Case of Idiopathic Hypoparathyroidism, J. Clin. Investigation **7**:183, 1929.

39. Albright, F.: The Parathyroids: Physiology and Therapeutics, J. A. M. A. **117**:527 (Aug. 16) 1941.

comment, therefore, that during the second balance experiment on our patient urinary calcium excretion was only 3 to 5 mg. daily, although three estimations of the serum calcium during this period gave figures of 8.8, 10.1 and 10.0 mg. per 100 ml. Again, since the patient's discharge from hospital, the calcium content of a midmorning specimen of urine has been determined seven times and was less than 2 mg. per 100 ml. on four occasions, although the serum calcium levels were within normal limits. It would seem that the Sulkowitch test might prove a fallacious guide in treatment, and this has been the experience of some physicians (Sevringhaus and St. John [40]).

The elevated serum alkaline phosphatase persisted throughout the period of treatment in our patient, but the level tended to decline when the serum calcium had been normal for a considerable time. There was no close correlation between the serum calcium level and the serum alkaline phosphatase activity; the correlation between the phosphatase and the serum inorganic phosphate level was perhaps a little closer. Since the blood phosphatase is believed to take part in the calcification of bone, it is interesting to note that some increased sclerosis of the long bones was present in our case. Albright [39] stated that the serum phosphatase was always normal or low in hypoparathyroidism; we cannot agree.

We were puzzled by the negative phosphorus balance of the first balance experiment. Since there is evidence that parathyroid extract acts primarily by increasing renal excretion of phosphorus (Albright and Ellsworth [38]; Albright, Bloomberg, Drake and Sulkowitch [41]), it might have been expected that a diminution or absence of this hormone would be accompanied with diminished renal excretion of phosphate, with phosphorus retention in the body. Further study of the literature revealed that, although patients with hypoparathyroidism are usually in calcium balance (Emerson and others [4]; McQuarrie and others [10]; Leonard [17]), a negative calcium balance can occur if the dietary calcium and phosphorus are low (McQuarrie and others [10]), while the results of phosphorus balance studies have been variable. Thus, Anderson and Lyall,[26] in their cases of postoperative hypoparathyroidism, recorded positive phosphorus balances at both high and low levels of phosphorus intake. Emerson and his co-workers [4] in one case of idiopathic hypoparathyroidism reported a positive phosphorus balance with a low calcium, high phosphorus intake and a slightly negative phosphorus balance with a high calcium, low phosphorus diet. McQuarrie and his associates,[10] in their patient with idiopathic hypoparathyroidism, found a negative balance for both calcium and phosphorus on a diet low in these and other minerals, but a positive calcium and phosphorus balance was obtained on an "adequate mineral diet." On the other hand, Albright and Ellsworth,[38] in a case of idiopathic hypoparathyroidism, reported a negative phosphorus balance on a high phosphorus diet and a positive balance when the phosphorus intake was low. In our first balance experiment the average daily intakes of calcium and phosphorus were normal (937 and 1,251 mg.,

40. Sevringhaus, E. L., and St. John, R.: Parathyroid Tetany Treated with Massive Doses of Vitamin D, J. Clin. Endocrinol. **3**:635, 1943.

41. Albright, F.; Bloomberg, E.; Drake, T., and Sulkowitch, H. W.: A Comparison of the Effects of A.T. 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypoparathyroidism, J. Clin. Investigation **17**:317, 1938.

respectively). Since previous studies of phosphorus balance in similar patients have given conflicting results, we feel that our findings do not invalidate the diagnosis.

The second balance study was performed when the patient was on a high protein diet, with a considerably raised calcium and phosphorus intake, and was also receiving 150,000 international units of calciferol daily. Since there is evidence that vitamin D augments not only calcium absorption but also urinary excretion of phosphorus (Albright and Sulkowitch [42]; Albright and others [41]) an increase in the amount of calcium retained associated with a rise in the urinary phosphorus output could occur; such proved to be the case.

While our patient was being investigated, we took the opportunity to study briefly some aspects of his magnesium metabolism. The serum magnesium was always within normal limits, varying between 1.7 and 3.8 mg. per 100 ml. The injection of parathyroid extract appeared to be without effect either on the serum magnesium level or on the rate of urinary excretion of magnesium. The first balance experiment showed an average retention of 27 mg. of magnesium daily, but in view of the difference between the magnesium contents of the two diets analyzed (222 and 102 mg.) the result is of little importance.

Treatment.—Except for administration as an emergency measure, parathyroid extract has little place in the treatment of chronic hypoparathyroidism, though it may prove useful for limited periods (Cantarow and others [8]; Franco [9]). In most cases the hypocalcemia can be corrected by administration of extra calcium by mouth in combination with calciferol or dihydrotachysterol. Restriction of the phosphorus intake, when practicable, is helpful (Anderson and Lyall [26]).

Dihydrotachysterol appears to have been used more frequently than calciferol in the treatment of hypoparathyroidism and was recommended by Albright [39]; McLean,[43] however, in a very full review stated that there is no convincing evidence that dihydrotachysterol is superior to calciferol, provided the latter is used in comparable dosage. Himsworth and Maizels [16] reported that serum calcium levels tended to be more erratic when dihydrotachysterol was used than when control was established with calciferol, and Schultzer and Christensen [44] noted that the average maintenance dose of calciferol required for 11 patients with chronic tetany was slightly less than that of dihydrotachysterol. Satisfactory results with calciferol have also been reported by Klatskin,[45] Anderson and Lyall [26] and Mortell.[14] The dosage of calciferol used has ranged from 30,000 to 400,000 international units daily. Sevringhaus [2] considered that control by dihydrotachysterol was cheaper than by vitamin D in the United States at that time, but later (Sevringhaus and St. John [40]) the reverse was apparently the case. It seemed to us that dihydrotachysterol was likely to prove dearer at present prices in Great Britain.

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42. Albright, F., and Sulkowitch, H. W.: The Effect of Vitamin D on Calcium and Phosphorus Metabolism: Studies on 4 Patients, J. Clin. Investigation **17**:305, 1938.

43. McLean, F. C.: Activated Sterols in the Treatment of Parathyroid Insufficiency: Review, J. A. M. A. **117**:609 (Aug. 23) 1941.

44. Schultzer, P., and Christensen, B. C.: Treatment of Parathyroid Tetany with Vitamin D_2, Acta med. Scandinav. **123**:362, 1946.

45. Klatskin, G.: On the Actions of Crystalline Vitamin D_2 (Calciferol) in Chronic Parathyroid Tetany, J. Clin. Investigation **17**:431, 1938.

We have found no reference to the effects produced on the serum calcium and inorganic phosphate levels in other cases of hypoparathyroidism by increasing the protein intake. In our patient it would perhaps have been possible to produce the same effect by raising the dosage of calciferol still higher, but we feel that the apparent effect of the protein is of interest and such a measure might prove useful in other cases. It may be objected that the effect was not due to the increase in protein consumption but to the coincident rise in calcium intake from about 3 to about 4 Gm. daily (of which 2 Gm. was in the form of calcium lactate). This view seems unlikely, especially as the phosphorus intake was increased simultaneously from about 1.4 to about 3 Gm. daily, which might well hinder calcium absorption. Nevertheless, we cannot exclude the possibility. Unfortunately, it was not realized at the time that the change in protein intake would double the dietary calcium content, and a corresponding reduction in the dosage of calcium lactate was not made.

SUMMARY

A case of idiopathic hypoparathyroidism is described. The main clinical features were chronic tetany, epileptiform attacks, stunted growth, retarded eruption of teeth, early bilateral cataracts and symmetrical intracerebral calcification. The serum calcium level and urinary calcium excretion were low. The serum inorganic phosphorus level was high, and the serum alkaline phosphatase activity was increased. No cause for the condition was found.

Initial treatment with calcium lactate and large doses of calciferol was without effect on the condition, but an increase in the protein intake, together with the continued administration of calcium lactate and calciferol, was followed by disappearance of the tetany and a return to normal of the serum calcium.

Before treatment a balance experiment showed that the patient was in slightly positive calcium balance and more markedly negative phosphorus balance. A second balance experiment, when treatment had become effective, showed a considerable increase in the amount of calcium retained, but the loss of phosphorus continued at a higher rate. The return of the serum calcium to normal was associated with a fall of the serum inorganic phosphorus and a diminution of the serum alkaline phosphatase activity.

Fourteen months after the initial correction of the hypocalcemia there had been no return of tetany and no further epileptiform attacks; normal serum calcium levels were being maintained with administration of calcium chloride and calciferol, although the protein intake had been allowed to revert to normal. There was little change in the teeth; the intracerebral calcification was apparently unchanged, but there was some evidence of regression of the cataracts in both eyes.

Dr. H. P. Brody, Physician to the Royal Infirmary, Sheffield, referred this case to the Medical Professorial Unit.

Drs. T. Lodge and R. Steiner made the roentgenograms and the reports thereon. Mr. W. Ingman made the ophthalmic examinations and reports. Mr. J. J. Hodson made the dental examinations and reports and Mr. R. Rastall the dental photographs and roentgenograms. Miss M. Mathers and Miss S. J. S. Dunthorne prepared the diets. Mr. D. A. Podmore analyzed diets and excreta. Mr. H. Brown and Miss J. M. O'Regan assisted with the blood analyses. Mr. A. L. Watson prepared prints from the roentgenograms of the skull. Mr. J. S. V. Larway and the staff of the Photographic Department made the photographs and Mr. A. S. Foster the chart.

ALLERGIC GRANULOMA OF THE LUNG

Clinical and Anatomic Findings in a Patient with Bronchial Asthma and Eosinophilia

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THE ALLERGIC basis of certain granulomatous alterations in tissue is receiving increasing recognition, although many of the entities are still ill defined and much of the evidence is indirect. Adequate criteria exist for the identification on morphological grounds of suspected lesions, and there is often satisfactory correlation with the clinical picture. Churg and Strauss [1] used the term "allergic granulomatosis" to characterize a group of vascular and extravascular lesions occurring in periarteritis nodosa in association with bronchial asthma and hypereosinophilia. Other cases on record [2] probably belong to the same category. Anatomic changes conforming to the general category of allergic reactions in tissue have, furthermore, been described in the lungs in those rare instances of Loeffler's disease which were studied at autopsy.[3]

In the following report of a case, allergic granulomas of the lung were observed at autopsy in a man who died of asphyxia 10 days after his first attack of bronchial asthma.

REPORT OF A CASE

The patient, M. T., was a white man 49 years of age who, except for recurrent seasonal attacks of late summer hay fever, had been in good health prior to his present illness. The family history revealed a high incidence of asthma in close relatives. Information regarding parasitic infestation was not elicited. The patient had not used nasopharyngeal drops or spray medication.

This study was aided by a grant from the Aaron W. Davis Foundation.

From the Department of Laboratories and the Medical Service, Lebanon Hospital.

1. Churg, J., and Strauss, L.: Allergic Granulomatosis, abstracted, Am. J. Path. **25**:817, 1949.

2. (*a*) Hejtmancik, M. R.; Schofield, N. D., and Herrmann, G. R.: Allergic Cardiovascular Disease, with Report of 2 Cases of Periarteritis Nodosa, Am. J. M. Sc. **217**:187-193, 1949. (*b*) Weinberg, T.: Periarteritis Nodosa in Granuloma of Unknown Etiology: Report of 2 Cases, Am. J. Clin. Path. **16**:784-791, 1946. (*c*) Zuelzer, W. W., and Abt, L.: Disseminated Visceral Lesions Associated with Extreme Eosinophilia: Pathologic and Clinical Observations on Syndrome of Young Children, Am. J. Dis. Child. **78**:153-181 (Aug.) 1949.

3. (*a*) Bayley, E. C.; Lindberg, D. O. N., and Baggenstoss, A. H.: Loeffler's Syndrome: Report of a Case with Pathological Examination of the Lungs, Arch. Path. **40**:376-381 (Nov.-Dec.) 1945. (*b*) Bergstrand, H.: Morphological Equivalents in Polyarthritis Rheumatica, Periarteritis Nodosa, Transient Eosinophilic Infiltration of the Lung and Other Allergic Syndromes, J. Path. & Bact. **58**:399-409, 1946. (*c*) Broch, O. J.: A Case of Transient Pulmonary Infiltration with Eosinophilia, with Fatal Issue After Treatment by Adrenalin Spray for Asthma, Acta med. Scandinav. **113**:311-320, 1943. (*d*) Smith, J. F.: Disseminated Focal Necrosis with Eosinophilia and Arteritis in a Case of Asthma (Loeffler's Syndrome?), J. Path. & Bact. **60**:489-494, 1948. (*e*) von Meyenburg, H. V.: Das eosinophile Lungeninfiltrate: Pathologische Anatomie und Pathogenese, Schweiz. med. Wchnschr. **72**:809-811, 1942.

He first became ill with a sudden attack of shortness of breath, cough and wheezing nine days before his admission to the hospital. He was seen by his family physician, who made a diagnosis of bronchial asthma and gave him an injection of epinephrine subcutaneously; it brought relief in a short time. However, the attacks recurred, and the response to epinephrine became less satisfactory. The attacks grew more frequent; severe cyanosis set in, and he had difficulty in raising small amounts of thick tenacious sputum. After nine days at home, hospitalization was advised, since his general condition deteriorated rapidly.

Following admission, the patient received two injections of 0.06 Gm. of phenobarbital sodium intramuscularly, 1 cc. of ether in oil intramuscularly and oxygen by nasal catheter. There was no response to therapy, and he lapsed into a deep coma. At the time of examination in consultation by one of us (A. R.) the patient was moribund. He was in deep coma and presented a generalized grayish blue cyanosis. Respirations were regular, 26 per minute, but it was noticed that neither the wall of the chest nor the abdomen moved perceptibly with respirations. No breath sounds were heard, but there were a few sibilant rales and rhonchi throughout the pulmonary fields. Heart sounds were good and not rapid; the pulse rate was 80 per minute and regular. The blood pressure was 120/70. The neurological examination gave normal results. Oversedation and a cerebral accident seemed unlikely causes for his coma. It was concluded that the coma was due to cerebral anoxia and was part of the general hypoxia resulting from lack of oxygenation of the blood consequent to obstruction of the tracheobronchial tree. Regardless of the nature of the obstruction, it was apparent that the only possible therapeutic measure which could be of any avail was bronchoscopy; before this could be performed the patient died, one-half hour after he was first seen in consultation and 10 days after his first attack of bronchial asthma.

It was not possible to carry out adequate laboratory studies. No roentgenograms were taken during the 24 hours in the hospital. Blood cultures were not made. One blood count revealed 13.6 Gm. of hemoglobin and 16,200 white blood cells, with 52 per cent polymorphonuclear leukocytes, 16 per cent band cells, 22 per cent lymphocytes and 10 per cent eosinophils.

Autopsy Observations.—The body was that of a well developed, well nourished, heavily built white man. Rigor mortis was complete. Purplish cyanosis of the head, neck and upper part of the trunk was present. There was no edema, icterus or cutaneous hemorrhage.

Body Cavities: There was no increase of fluid in the peritoneal, pleural or pericardial cavities. A few firm fibrous adhesions were present between the upper lobe of the left lung and the pericardium.

Cardiovascular System: The heart weighed 450 Gm. The myocardium was firm and contracted. The color was reddish purple. The epicardium was smooth and glistening. The cardiac chambers were normally formed; the valves showed occasional tension thickenings, especially in the mitral and aortic leaflets. The orifices of the coronary arteries and the vessels themselves were widely patent; occasional flat intimal atheromatous plaques were present. The aorta and its main subdivisions presented only a moderate degree of atheromatosis. The venae cavae were greatly distended with blood and postmortem clots.

Respiratory System: The mucosa of the epiglottis and larynx was congested; there was a small nodule on the epiglottis, 0.5 cm. in diameter, which had the appearance of circumscribed edema. The tracheobronchial tree below the vocal cords was filled by a castlike mass of greenish gray mucopurulent tenacious material which extended into the subdivisions of the third and fourth order. This material was rubbery and could be lifted out almost in one piece. Cultures revealed hemolytic Streptococcus and Hemophilus influenzae. Hilar lymph nodes were calcified. The lungs together weighed about 1,200 Gm. Lobulation was normal. The color was deep reddish purple; the consistency was firm, and there was a moderate degree of atelectasis in all lobes. Several emphysematous areas were also present. The pleural surfaces appeared dry and granular in areas, particularly over the nodular masses described below.

The most conspicuous alterations in the lungs were two tumor-like masses (fig. 1), one in the upper lobe of the left lung anteriorly and one at the base of the upper lobe of the right lung. The lesion in the upper lobe of the left lung was located in the infra-apical portion near the anterior margin. It was spherical, 5 cm. in diameter, very hard in consistency and raised 2 cm. above the surface of the surrounding lung at the point of maximum elevation; it exerted slight pressure on the neighboring wall of the trachea. The pleura over this mass was covered by flaky fibrinous exudate and was deeply congested. Section through this lesion disclosed a some-

what dirty yellow central portion, composed evidently of necrotic tissue, and a shell 3 to 5 mm. wide of brownish gray cellular tissue which was quite sharply demarcated from the surrounding engorged parenchyma of the lung.

The nodule in the upper lobe of the right lung was smaller than that in the left. It was about 1.5 cm. in diameter but was in every other essential similar in macroscopic appearance to the mass in the left lung.

Liver and Bile Ducts: The liver weighed 2,025 Gm. It was normal in size and contour. The capsule was smooth; the consistency was somewhat firmer than normal, and the color was purplish brown. On section, normal lobular markings were exaggerated by congestion. The gallbladder and bile ducts did not show any significant changes.

Spleen: The spleen weighed 175 Gm. It was normal in form; the consistency was increased, and the color was dark purple. On section the lymph follicles were conspicuous.

Urinary System: The left kidney weighed 220 Gm., the right 175 Gm. Consistency was firmer than normal; the color was cyanotic purplish red. The capsule could be removed easily, revealing

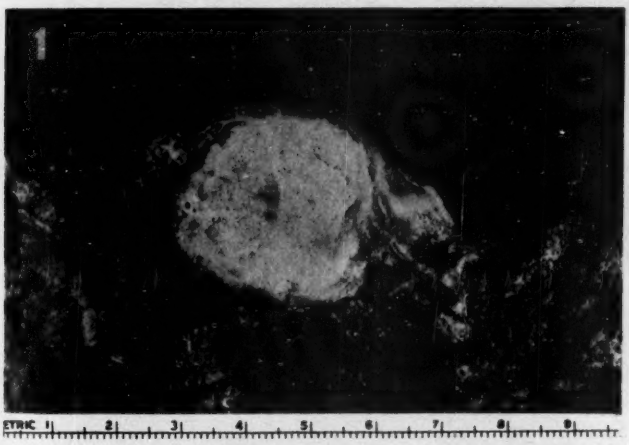

Fig. 1.—Appearance on cut section of mass in upper lobe of left lung. Note large grayish white area of necrosis. Thin zone of compressed and inflamed pulmonary parenchyma surrounds entire lesion.

a smooth surface. Markings were normal on the cut surfaces. Pelves, ureters and bladder were normal.

The pancreas, genital organs, gastrointestinal tract and brain did not show any significant alterations.

Endocrine Glands: Pituitary and thyroid glands did not show any significant macroscopic abnormalities. The thymus appeared to have undergone complete regression. The inner zone of the adrenal cortex appeared congested. These glands were otherwise normal in appearance.

Histopathological Findings.—Sections through the nodular masses in the lung revealed a central zone of necrosis, surrounded by a dense cellular inflammatory infiltrate (fig. 2). The vast majority of cells composing this infiltrate were eosinophilic polymorphonuclear cells. The transition from infiltrate to surrounding lung was quite abrupt.

The bronchioles within the infiltrate and nearby were occluded by mucous plugs containing large numbers of eosinophils (fig. 7). The muscle fibers in the walls of the small subdivisions of the bronchi were conspicuous and appeared hypertrophied.

Branches of the pulmonary artery at the edge of the infiltrate showed varying degrees of involvement of all coats. The milder forms presented merely a few eosinophils in the adventitia.

media or intima. The severest forms presented dense infiltrates in all coats, edema with separation of the fibers in the muscularis, collagen swelling in the adventitia and intimal thickening due to edema and cellular infiltrate which sometimes completely occluded the lumen (fig. 3).

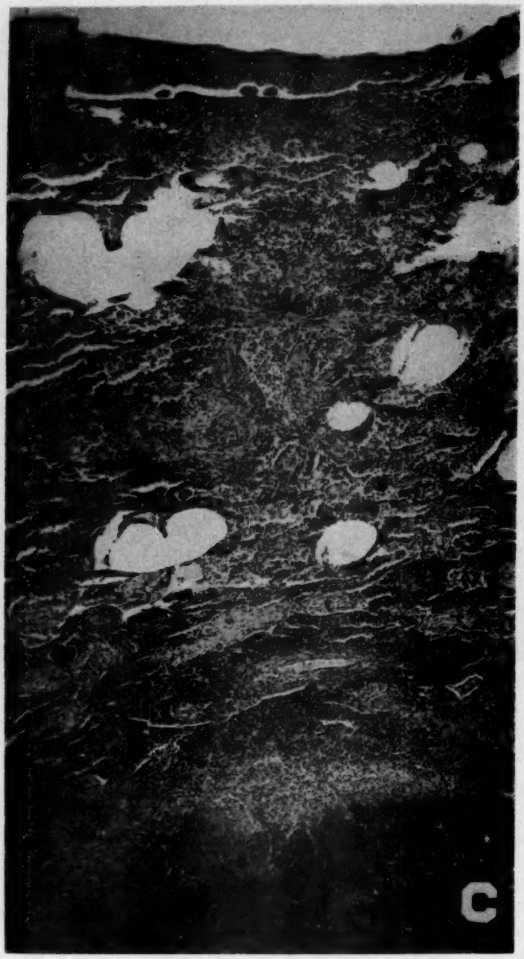

Fig. 2.—Low power photomicrograph of area extending from pleura (*A*) to margin of necrotic tissue (*C*). Fresh fibrinous pleuritis on surface (*A*); interstitial pneumonitis with eosinophils (*B*); necrotic zone (*C*). × 20.

The necrotic center of the lesion was sharply separated from the non-necrotic portion of the infiltrate. The necrosis was not complete, so that some details of nuclei and cells could be discerned; the general appearance was somewhat reminiscent of that of caseous necrosis. Occasionally one could recognize an obliterated artery within the area of necrosis; these vessels were conspicuously brought out by stains for elastic tissue.

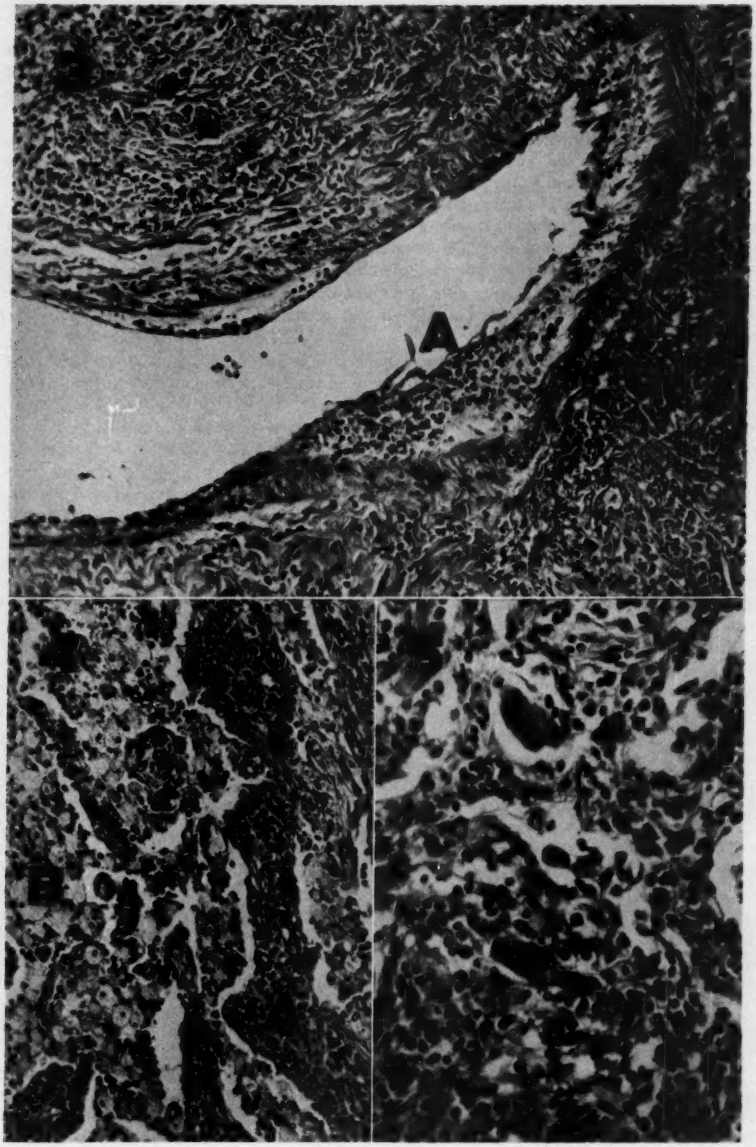

Fig. 3.—Small branch of pulmonary artery showing allergic endarteritis at *A*, widening of intima due to cellular infiltrate of eosinophils and plasmacytes and swelling of collagen fibers and edema. × 180.

Fig. 4.—Interstitial pneumonitis. Conspicuous widening of alveolar septums (*A*) with infiltration by eosinophils and plasmacytes. Numerous lipophages in alveolar lumens (*B*). × 180.

Fig. 5.—Area of pneumonitis with multinucleated giant cells, eosinophils and plasmacytes. × 350.

One of the striking features of the lesion was the presence of numerous areas of dark, almost homogeneous purplish pink material in haphazard or structureless arrangement. Examination of these areas at high magnifications revealed innumerable eosinophilic granules evidently resulting from the disintegration of large numbers of closely packed eosinophils (fig. 9).

Other cytological elements taking part in the formation of the lesion were plasma cells, lymphocytes, histiocytes and occasionally multinucleated giant cells. The giant cells were present mainly at the periphery and in the lung tissue immediately surrounding the lesion and appeared to belong to the category of foreign body giant cells. They contained as many as eight or 10 nuclei unevenly distributed through the cytoplasm (fig. 5). Alveolar walls were decidedly thickened and infiltrated by eosinophils, lymphocytes and plasma cells (fig. 4*A*). Numerous alveoli contained clusters of phagocytes filled with sudanophilic droplets (fig. 4*B*).

Hemorrhage was notably absent; only infrequent extravasations of blood could be found in the alveoli. A mild degree of banal pneumonitis was present in some areas in the lung tissue contiguous to the lesion.

The pleura directly over the lesion was infiltrated by eosinophils and lymphocytes; its capillaries were conspicuously engorged, and there were deposits of fibrin on the surface. In other areas the pleural fibrinous deposit was partly organized.

In random sections taken from different parts of the involved lung, the subdivisions of the bronchial tree were invariably occluded by mucous plugs in which numerous eosinophils and polymorphonuclear cells were embedded. Occasional foci of ordinary bronchopneumonia were present, with infiltrates consisting entirely of polymorphonuclear leukocytes. Several portions of the lung were strikingly emphysematous. Numerous arterioles showed hypertrophied muscular coats. Silver stains disclosed some residual architecture of pulmonary tissue in the necrotic zone.

In one section several lesions were present at the periphery of the infiltrate which were unusual and merit separate description. These were lesions of the alveolar wall that might be described as interstitial. The lesions consisted of prominent bulbous and fusiform swelling, from 15 to 20 times the thickness of normal alveolar walls. The alveolar lining cells were maintained on the periphery, and the enlargement appeared due to edema of the delicate collagen fibers; there seemed to be an accumulation of edema fluid or increased amounts of ground substance among these fibers. Slight infiltrations by plasma cells and eosinophils and an occasional foam cell were scattered throughout these lesions (fig. 8).

Section of the nodule in the epiglottis revealed acute nonspecific inflammatory reaction in the submucosa. The infiltrate consisted almost entirely of polymorphonuclear leukocytes; however, a few eosinophils and plasma cells were present.

Section of a hilar lymph node showed conspicuous infiltration by eosinophils and many plasma cells. No vascular lesions were seen.

The bone marrow revealed a striking increase in eosinophilic granulocytes, particularly eosinophilic myelocytes. In many fields there was a great preponderance of these cells.

One section from the pyloric portion of the stomach revealed a freshly hemorrhagic inflammatory lesion. The surface was eroded, and the submucosa showed marked edema, swelling of collagen bundles and a dense infiltration by inflammatory cells, chiefly polymorphonuclear forms with some eosinophils. The blood vessels were strikingly dilated and engorged; several had ruptured with local hemorrhage. The inflammatory infiltrate extended to a lesser degree through the muscular coat and the serosa.

Foci of infiltration by eosinophils were seen in the muscularis and serosa of the small intestine.

In several sections of epicardium there were conspicuous perivascular infiltrates by eosinophils; these surrounded some of the veins, as well as arteries, and were present in the fat tissue around the major vessels on the surface of the heart. Perivascular infiltrates within the myocardium could not be found. Occasional perineural infiltrates of eosinophils could be seen about the larger nerves of the epicardium. In one or two places the infiltrate extended for a short distance into the myocardium. Sometimes the reaction reached the surface of the epicardium, producing small surface granulomas. Occasionally, a long collagen band with fibrinoid alteration and palisaded large histiocytes was found in the epicardium.

There were some fields in the spleen in which the number of eosinophils appeared to be moderately increased. In general, however, the histological pattern was that of acute congestion.

The pleural surface of the diaphragm showed a nonspecific fibrinous pleuritis with a few eosinophils. However, the diaphragmatic muscle was densely infiltrated by eosinophilic leukocytes (fig. 6).

Brain, thyroid, testes, prostate, gallbladder, appendix, liver, kidney, pancreas, voluntary muscle (abdominal wall) and pituitary were essentially normal. There was no evidence of recent or old infestation by parasites.

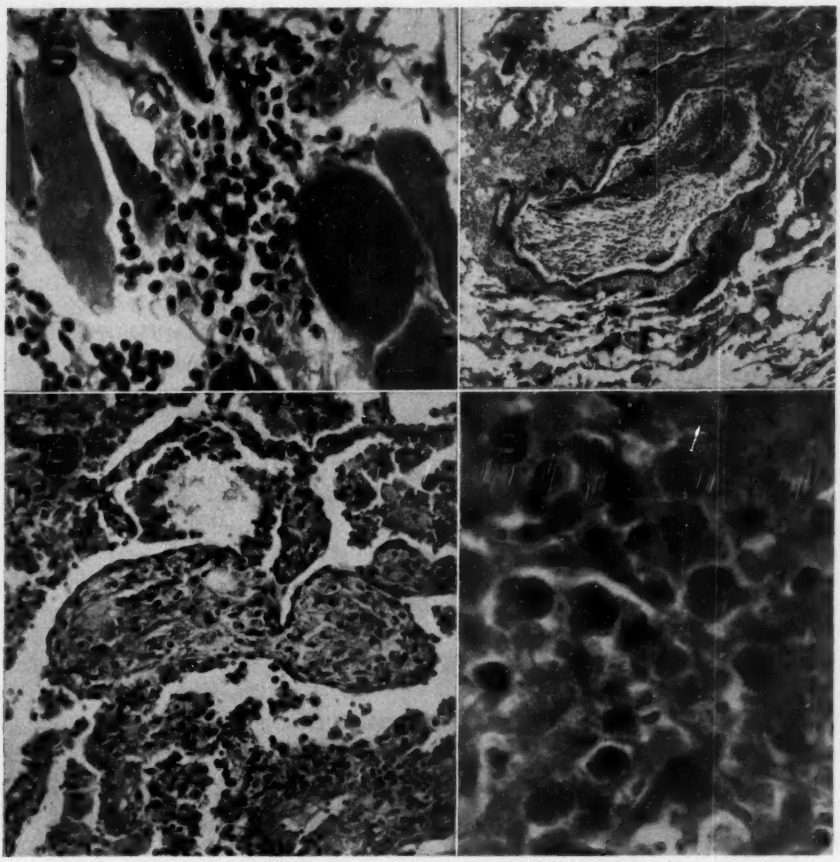

Fig. 6.—Diaphragm. Infiltrate composed of eosinophilic leukocytes. × 350.

Fig. 7.—Low power photomicrograph of bronchiole. Total occlusion by mucus containing numerous eosinophils. × 20.

Fig. 8.—Bulbous interstitial lesion in lung (see text). Bulbar enlargement of alveolar wall; swelling of collagen fibers; infiltration by eosinophils and lipophages; swelling of endothelial cells. × 180.

Fig. 9.—High power photomicrograph of area inside necrotic zone (photographed under reduced illumination). "Corpses" of eosinophils. Details of cell outline of eosinophils and intracytoplasmatic granules can still be made out despite failure of their nuclei to stain. × 900.

Anatomic Diagnoses.—The anatomic diagnoses were as follows: (1) allergic granulomas of upper lobes of left and right lungs; infiltrates of eosinophilic leukocytes in epicardium, stomach,

small intestine, diaphragm, bone marrow, spleen and lymph nodes; (2) status asthmaticus (clinical), with obstruction of tracheobronchial tree by mucopurulent plugs; (3) acute fibrinous pleuritis of upper lobe of left lung; fibrous pleuropericardial adhesions of left lung; (4) calcification of hilar lymph nodes; (5) moderate arteriosclerosis of coronary arteries and aorta, and (6) severe passive congestion of viscera, while the (7) cause of death was asphyxia.

COMMENT

The anatomic examination of the lungs disclosed two tumor-like masses which presented microscopically exudative pneumonitis with necrosis and numerous vascular lesions. A careful search of other organs disclosed, in addition, microscopic infiltrates by eosinophils in the epicardium, diaphragm, intestinal wall, hilar lymph nodes and stomach; the splenic pulp revealed foci with increased numbers of eosinophils and sections of bone marrow disclosed hyperplasia with a striking predominance of the eosinophilic granulocytes in varying stages of maturity.

The pattern of organization of the pulmonary granulomas in our patient was similar to that described by Meyer-Doerkin,[4] Zuelzer and Abt,[2c] Bergstrand,[3b] Churg and Strauss,[1] Bayley, Lindberg and Baggenstoss,[2a] Hejtmancik, Schofield and Herrmann [2a] and Weinberg [2b] in a variety of clinical states in adults and children. An allergic mechanism has been invoked by most of these authors in the causation of the lesions. Similar granulomas in the vermiform appendix were observed by one of us (J. C. E.) in material accessioned at the Armed Forces Institute of Pathology; evidence of parasitic infestation could not be obtained in most of these cases. Wenger [5] has recently reported similar alterations in appendixes; he found evidence of infestation by Strongyloides and stressed the role of hypersensitivity in the production of the granulomas.

The histopathological features of these granulomas favor their interpretation as manifestations of allergic phenomena in tissue.[6] The essential components are necrosis, cellular infiltrates in which eosinophilic leukocytes predominate, edema and fibrinoid swelling of collagen and vascular changes. Epithelioid and giant cells occur less regularly; they probably belong to the reactive changes which follow the initial stages in the establishment of the granuloma. Search for bacteria is futile. Charcot-Leyden crystals were not found in our material; they have been observed in similar lesions by others.[2b,c]

The centers of the lesions present several interesting morphological aspects. The necrobiosis of various tissue elements in these areas is probably primary, i. e., a direct allergic injury, and not merely a secondary effect of vascular damage or toxic substances in the ordinary sense. The central portion of the granuloma presents a deep purplish pink color in hematoxylin and eosin preparations. Examination with the oil immersion objective under reduced illumination reveals "corpses"

4. Meyer-Doerkin, G.: Zur Frage der Sepsis mit allergischer Reaktion, Virchows Arch. f. path. Anat. **292**:374-383, 1934.

5. Wenger, F.: Necrosis eosinofílica y seudotubérculos de origen parasitario en el apéndice vermicular, Rev. sudam. morfol. **6**:36-55, 1948.

6. Bohrod, M. G.: Classification of the Histologic Reactions in Allergic Diseases, Am. J. Med. **3**:511-522, 1947. Ehrlich, J. C.: Erysipelothrix Rhusiopathiae Infection in Man: Report of Case with Cutaneous Bullae, in Which Cure Was Effected with Penicillin, Arch. Int. Med. **78**:565-577 (Oct.) 1946.

of eosinophilic leukocytes (fig. 9) and sometimes "sludged" masses of eosinophilic granules from disintegrating or disintegrated eosinophils. Stains for elastic and argentophilic fibers bring out some details of residual architecture of the tissue in the necrobiotic region. The retention by the dead eosinophils of their cell form is noteworthy; it is consistent with the observation [7] that the eosinophilic leukocyte of the blood is the "toughest" of the leukocytes—a fact taken advantage of in the various technics for chamber counts of eosinophils.

Special attention is directed to another lesion in the lungs of our patient (fig. 8). It consisted essentially of bulbous swelling of the alveolar walls, resulting from interfibrillar edema or increase of ground substance, collagen fiber swelling and infiltration by eosinophils, occasional plasma cells and foam cells and capillary engorgement. The presence of these lesions in the vicinity of the infiltrate and their absence throughout the lung elsewhere suggest that they may represent a form of pulmonary parenchymal lesion in allergic disease; the histological characteristics are consistent with such a concept. Elsewhere the interstitial pneumonitis was characterized by widening of alveolar walls, cellular infiltrates composed of eosinophils with lymphocytes and occasional plasma cells and capillary engorgement (fig. 4).

Our patient was not observed clinically or roentgenographically under conditions which might have led to the diagnosis of Loeffler's disease; it is likely that such a diagnosis would have been arrived at in view of the asthma, eosinophilia and pulmonary findings. The demonstration of allergic granulomas of the lung and allergic changes in other organs in our case, as well as in other reported instances of Loeffler's disease, makes it quite clear that the concept of Loeffler's disease is too narrowly focused on the pulmonary aspects of an essentially systemic disturbance.

One of the characteristic clinical features of the Loeffler syndrome is the evanescent nature of the pulmonary lesions. This has led some observers to hypothesize the existence of an edema of the pulmonary tissue analogous to urticaria of the skin.[8] However, the observations of von Meyenburg [3c] and of Bayley, Lindberg and Baggenstoss [3a] and the findings in our case suggest that the pulmonary lesions can be of much longer duration than the usual clinical and roentgenologic findings would lead one to suspect. Of course, milder degrees of anatomic involvement of the lungs may occur, and some lesions may undergo complete resolution in a relatively short time. It is possible, furthermore, that the pulmonary lesions may in some instances be restricted to an eosinophilic pneumonitis without necrotic or vascular components. Such infiltrates were observed in our patient, but in organs other than the lungs. Roentgenographic lesions in Loeffler's disease have been described as small irregular rosette or linear plaques.[9] The case described by Bayley, Lindberg and Baggenstoss [3a] showed at necropsy tumor masses similar

7. Speirs, R. S., and Meyer, R. K.: The Effects of Stress, Adrenal and Adrenocorticotrophic Hormones on the Circulating Eosinophils of Mice, Endocrinology **45**:403-429, 1949.

8. Vaughn, W. T., and Hawke, E. K.: Angioneurotic Edema with Some Unusual Manifestations, J. Allergy **2**:125-129, 1931.

9. Henell, H., and Sussman, M. L.: Roentgen Features of Eosinophilic Infiltration of the Lungs, Radiology **44**:328-334, 1945.

to those reported herein, but in von Meyenburg's case [36] some of the lesions were essentially in the category of eosinophilic pneumonitis without conspicuous necrotic or vascular components.

It appears justified to redefine the concept of Loeffler's disease as a form of systemic allergic disease of mild character and good prognosis in which the chief manifestations are confined to the pulmonary system. It is necessary to bear in mind, however, that severer forms of allergic disease may develop and that the involvement of extrapulmonary organs and the general vascular system may overshadow the pulmonary changes; some of these cases may terminate fatally, usually with anatomic findings of periarteritis nodosa and allergic granulomatosis.[1]

SUMMARY

The necropsy observations on a patient with bronchial asthma and eosinophilia who died in status asthmaticus are presented. Allergic granulomas were present in the lungs; vascular lesions classifiable as allergic arteritis were found in association with the pulmonary lesions; histological studies revealed numerous foci of infiltration by eosinophilic leukocytes in other sites, including the epicardium, diaphragm, small intestine, spleen and bone marrow.

The concept of a form of allergic disease of varying degrees of severity, manifested clinically by bronchial asthma, eosinophilia and pulmonary infiltrates, and anatomically by disseminated allergic granulomas and allergic vascular lesions, is discussed.

CHRONIC REGURGITATION JAUNDICE AS THE PRESENTING SIGN IN SARCOIDOSIS

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NUMEROUS cases of sarcoidosis have been described in the literature since the disease was first recognized as an entity in 1899. It is well known that the sarcoid lesions may be widely disseminated and frequently involve such structures as skin and mucous membranes, lymph nodes, lungs, bone, the uveoparotid tracts, spleen and liver. However, isolated sarcoidosis of the liver has been described in the literature comparatively infrequently, and in only two instances did we find reports of hepatic involvement with associated regurgitation jaundice. It is the purpose of this paper to present and discuss a case of sarcoidosis of the liver with chronic jaundice. The physical findings, laboratory data and course of this disease were similar to those seen in cholangiolitic cirrhosis of the liver.

REPORT OF CASE

R. M., a 25 year old Negro woman, was admitted to Michael Reese Hospital in September 1947, with complaints of nausea and vomiting for 24 hours and persistent jaundice for approximately seven years. Mild epigastric discomfort and moderate pruritus were present at the time of her admission. Her pertinent history dated back to February 1940, when she was admitted to another hospital with almost identical complaints. She was discharged in four weeks without residual jaundice. No definite diagnosis was made at that time.

She was readmitted to the same hospital in September 1943, with the same complaints, but the jaundice persisted after her discharge and has been constantly present, although varying in degree, since then. In April 1946, and again in May and June 1947, she experienced, besides nausea and vomiting, attacks of chills, fever and some swelling of the wrists and ankles. During these episodes her liver and spleen were prominently enlarged, but no ascites was noted. She stated that during the entire period since February 1940 she had almost constant itching of the skin, frequent bleeding from the gums and shortness of breath and had been told that she was anemic. She lost 15 to 20 pounds (7 to 9 Kg.) during this seven year period.

In June 1947, during a stay in the hospital, a rash developed on the nose and palms. This was diagnosed as secondary syphilis, and she received penicillin therapy. The rash cleared rapidly.

She had been a heavy drinker for the past two years, occasionally drinking as many as 10 "shots" a night. Apart from intolerance to fatty foods, her dietary intake was adequate and her appetite was good.

The essential physical findings on her admission were a temperature of 100.2 F. (rectum), a blood pressure reading of 110/80, palpable small, nontender lymph nodes in the posterior cervical and left supraclavicular regions and icteric scleras. The liver was greatly enlarged,

From the Department of Medicine and the Department of Hematological Research, Medical Research Institute, Michael Reese Hospital, Chicago.

extending downward approximately 10 cm. below the costal margin in the midclavicular line. It was not palpable to the left of the umbilicus and was hard, not nodular and nontender. The smooth, nontender spleen was palpable 6 cm. below the costal margin. No ascites was noted. There was no edema of the legs.

Laboratory tests performed at the time of her admission gave the following results: The roentgenogram of the chest was essentially normal. A flat plate of the abdomen revealed a large mass on the right side, suggesting liver. Excretion urography demonstrated normal kidneys, with no pathological changes in the genitourinary tract. A gastrointestinal series was entirely normal. The gallbladder filled and emptied normally.

Blood studies showed a hemoglobin concentration of 13.2 Gm., 4,380,000 red blood cells and 2,500 white blood cells, with 82 per cent polymorphonuclear forms, 4 per cent eosinophils, 9 per cent lymphocytes and 5 per cent monocytes. The sedimentation rate was 32 mm. (Wintrobe) corrected. There was a negative reaction to a test for sickling. The Kahn reaction was negative. The tuberculin reaction was weakly positive (1: 1,000 dilution). Urinalysis on her admission showed a trace of albumin, with 18 to 22 white blood cells per high power field, in a noncatheterized specimen. There was bilirubinuria, and urobilinogen excretion was slightly increased. Blood chemical studies showed 5 mg. of urea nitrogen, 6.1 mg. of uric acid, 78 mg. of glucose, 9.6 mg. of calcium and 5.2 mg. of phosphorus, per 100 cc. Alkaline phosphatase was 100.4 Huggins phenolphthalein units (normal, 3 to 15 units). Serum bilirubin measured 2.1 mg. and serum cholesterol 160 mg. per 100 cc., with 70 per cent esters. Thymol turbidity was 6.2 units and cephalin flocculation 2 + in 24 hours. Total protein measured 7.7 Gm. per 100 cc., with an albumin to globulin ratio of 1: 1.

There was little change in the patient's condition from her admission until surgical intervention three weeks later. She continued to be jaundiced, with a serum bilirubin level ranging from 2.1 to 3.1 mg. There was a persistent low grade fever (elevation in temperature to 99.8 F. orally daily). However, the initial symptoms of epigastric pain, nausea and vomiting disappeared in a few days, and she felt comparatively well.

Repeated blood counts continued to show moderate leukopenia (white blood cell count of about 4,500). There was a persistently elevated sedimentation rate, ranging from 29 to 52 mm. per hour. During her entire hospital stay the urine contained a trace of albumin, besides bilirubin and urobilinogen. A repeat urea nitrogen determination showed 6 mg. per 100 cc., and the alkaline phosphatase on September 11 was 102.4 units, but by September 29 it had dropped to 35 units. Both thymol turbidity and cephalin flocculation continued to be 2 to 4 +. Total protein determinations ranged from 6.2 to 8.0 Gm. per 100 cc., with the albumin to globulin ratio remaining at 1: 1. A marrow biopsy specimen revealed only slight erythroid hyperplasia. A biopsy specimen of a large supraclavicular node was reported as showing only reticulum cell hyperplasia.

Inasmuch as there was a difference of opinion about the significance of the right-sided abdominal mass, transabdominal pneumoperitoneum was performed, revealing on roentgenograms a large, soft tissue shadow which appeared to be separate from the liver at its upper margin.

On October 4 an exploratory laparotomy was performed. The large smooth liver was found occupying almost all the right side of the peritoneal cavity. A liver biopsy specimen was taken and reported by Dr. O. Saphir as revealing "a granuloma resembling Boeck's sarcoid" (figs. 1 and 2).

The patient was discharged to the outpatient service on October 26, with a diagnosis of sarcoidosis with involvement of the liver and spleen and chronic jaundice. Her condition was essentially unchanged.

She has been followed in the clinic since the time of her discharge. Her condition has remained relatively the same in most respects, except for the development of peripheral edema. This edema is associated with a persistently low serum albumin, ranging from 1.8 to 2.4 Gm. per 100 cc. It has been treated with high protein diet and occasional meralluride (mercuhydrin®) injections, with fairly good results. A laboratory check-up in December 1949 showed a serum bilirubin of 1.8 mg. per 100 cc., alkaline phosphatase of 85 units, 3 + cephalin flocculation, serum cholesterol of 248 mg., with 60 per cent esters, and total protein of 7.8 Gm. with 2.4 Gm. of albumin and 5.4 Gm. of globulin, per 100 cc. The red blood cell count was 4,850,000, the hemoglobin concentration 85 per cent and the white blood cell count 3,600. Numerous thrombocytes (platelets) were seen.

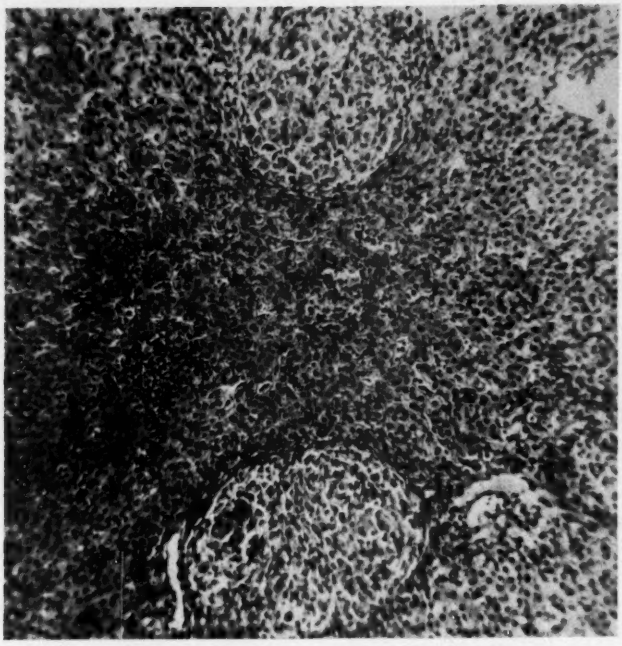

Fig. 1.—Biopsy specimen of liver: low power.

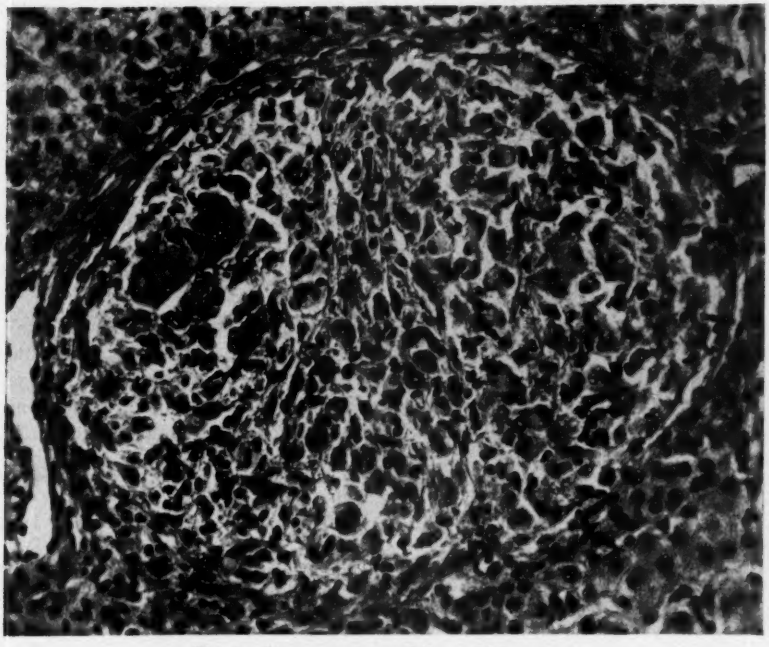

Fig. 2.—Biopsy specimen of liver: high power.

COMMENT

As knowledge of sarcoidosis has grown, many articles have appeared, discussing various aspects of this disease. However, the number of papers pertaining to hepatic involvement has been comparatively few, and those pertaining to sarcoidosis of the liver with the presenting sign of severe jaundice are rare indeed. In none of these reported cases was hepatic involvement an isolated finding. In most cases there was an associated involvement of the spleen, which is much more frequently involved than the liver, and usually the hepatomegaly was merely a part of the picture of widely disseminated sarcoidosis.

We were able to discover only two references in the literature, representing a total of four cases, dealing with sarcoidosis of the liver with jaundice, apart from several additional papers on Boeck's sarcoid with acholuric icterus due to symptomatic hemolytic anemia. Goeckerman,[1] in discussing 17 cases of sarcoidosis, described two patients with chronic jaundice. One was a 57 year old woman with a history of icterus of two years' duration. She had demonstrable involvement of the skin and lungs, and her spleen was enlarged. There was no mention of liver enlargement. The other patient was a 48 year old man who had intermittent attacks of jaundice, with vomiting of eight years' duration. In this patient there was splenomegaly, but again no hepatomegaly was mentioned. In neither of these patients was a liver biopsy or postmortem study performed. In neither case report were there any detailed laboratory studies pertaining to jaundice.

Longcope and Pierson[2] reported two cases of sarcoidosis with jaundice, in addition to two other cases of hepatomegaly without jaundice. One of their jaundiced patients was a 28 year old Negro man in whom, a few weeks after the onset of jaundice, a penile chancre developed, followed by secondary syphilis. The patient was treated for over one year with neoarsphenamine and bismuth. During this time there were three additional attacks of jaundice. Approximately one year after the first attack of jaundice, generalized lymph node enlargement was noted. The lungs showed diffuse fibrotic changes. Results of lymph node biopsy were diagnostic of sarcoidosis. The tuberculin reaction was negative. No liver biopsy was performed.

Longcope and Pierson also reported one additional case of disseminated sarcoidosis without enlargement of the liver or spleen in which transient jaundice developed on one occasion. The exact cause of the jaundice in this case remained unknown.

It is not the purpose of this paper to discuss cholangiolitic cirrhosis in detail. The classical paper by Watson and Hoffbauer[3] in 1946 has again brought this condition to general attention. This clinical picture is characterized by prolonged jaundice with fairly good maintenance of general health, pronounced hepatosplenomegaly, hypocholic stools, bilirubinuria and urobilinogen excretion in the urine.

1. Goeckerman, W. H.: Sarcoids and Related Lesions: Report of 17 Cases; Review of Recent Literature, Arch. Dermat. & Syph. **18**:237-262 (Aug.) 1928.

2. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**:223-296 (April) 1937.

3. Watson, C. J., and Hoffbauer, F. W.: Problem of Prolonged Hepatitis with Particular Reference to Cholangiolitic Type and to Development of Cholangiolitic Cirrhosis of Liver, Ann. Int. Med. **25**:195-277 (Aug.) 1946.

Hypercholesteremia and increase in blood alkaline phosphatase, with normal or only slight impairment of the reactions on flocculation tests, are noted.

A similar symptomatology may be found in xanthomatous biliary cirrhosis, except for the presence of xanthelasma and various xanthomas on the skin. The case described in this paper indicates that sarcoidosis should be included in the differential diagnosis. The findings in our patient differed somewhat from the typical picture of a cholangiolitic cirrhosis in that the blood cholesterol was normal and the thymol turbidity and cephalin flocculation tests showed pathological results. In general, however, the diagnosis of cholangiolitic cirrhosis was suggested by the findings, apart from the biopsy report.

It is interesting to note that hemolytic anemia may be associated with Boeck's sarcoid, as in cases reported by Crane and Zetlin,[4] Stats and his co-workers [5] and Bruschi and Howe.[6] In such cases the jaundice was characterized by an absence of bilirubinuria and a strongly increased indirect van den Bergh reaction. There was also splenomegaly in all instances. These cases are also quite rare but should not be difficult to distinguish from regurgitation jaundice such as we have described.

SUMMARY

Sarcoidosis of the liver with chronic regurgitation jaundice is a rare condition. A case is reported in which the syndrome closely resembled the picture of cholangiolitic cirrhosis. Sarcoidosis should be included in the differential diagnosis of cholangiolitic cirrhosis.

Medical Arts Building, Waco, Texas (Dr. Ross).

4. Crane, A. R., and Zetlin, A. M.: Hemolytic Anemia, Hyperglobulinemia and Boeck's Sarcoid, Ann. Int. Med. **23**:882-889 (Nov.) 1945.

5. Stats, D.; Rosenthal, N., and Wasserman, L. R.: Hemolytic Anemia Associated with Malignant Diseases, Am. J. Clin. Path. **17**:585-613 (Aug.) 1947.

6. Bruschi, M., and Howe, J. S.: Classification of the Hematologic Variations and Abnormalities Associated with Boeck's Sarcoid: Review of the Literature; Report of a Case of Thrombocytopenic Purpura Associated with Sarcoidosis, with Recovery Following Splenectomy, Blood **5**:478-489 (May) 1950.

SYNCOPE IN AORTIC STENOSIS

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SYNCOPE as a manifestation of aortic stenosis was first mentioned by Cowper in 1706.[1] He described a patient with this disease who "complained of great faintness, and now and then pain about the heart. . . ." The occurrence of syncope in aortic stenosis was not, however, generally recognized until recently. The reports of Gallavardin,[2] Gravier,[3] Marvin and Sullivan[4] and Contratto and Levine[5] have emphasized this symptom.

This report is based on a clinical analysis of 63 patients with aortic stenosis observed during a three year period at the Minneapolis Veterans Administration Hospital. A clinical diagnosis of aortic stenosis was accepted only when both an aortic systolic murmur and a thrill were present or when calcific aortic valves could be demonstrated by fluoroscopy. In 23 patients the diagnosis was proved at autopsy.

ANALYSIS OF PATIENTS WITH SYNCOPE

Syncope occurred in 16 of 63 patients (table 1). In 14 patients the syncopal episodes were associated with effort. The degree of exertion necessary for the production of an attack varied from mild to strenuous. Several patients could establish a definite level of exercise tolerance. Syncope was accompanied with premonitory symptoms in eight patients, and six of these patients could apparently abort a syncopal attack by rest. The warning symptoms included weakness, dyspnea, dizziness and angina pectoris. The duration of the attacks varied from a few minutes to one hour. Most of the patients had experienced episodes of

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Cowper, W.: Ossifications in the Coats of the Arteries, Philos. Tr. (abridged) **5**:341, 1721.

2. Gallavardin, L.: Les syncopes d'effort, Lyon méd. **151**:217, 1933; Trois nouvelles observations de "syncopes d'effort," ibid. **152**:581 1933; Les syndromes d'effort dans les affections cardioaortiques, J. de méd. de Lyon **14**:539, 1933; Syncopes d'effort dans le rétrécissement aortique, Médecine **16**:197, 1935; Le rétrécissement aortique non rhumatismal: Rétrécissement aortique pur ou très prédominant (d'après 50 observations personnelles), J. de méd. de Lyon **17**:593, 1936; Les syncopes d'effort dans le rétrécissement aortique: Leur fréquence et leur valeur diagnostique, Arch. d. mal. du cœur **30**:745, 1937.

3. Gravier, L.: (*a*) Syncopes d'effort solitares au cours du rétrécissement aortique pur non rhumatismal, J. de méd. de Lyon **15**:631, 1934; (*b*) Syncopes d'effort au cours d'accès angineux et rétrécissement aortique, ibid. **17**:615, 1936.

4. Marvin, H. M., and Sullivan, A. G.: Clinical Observations upon Syncope and Sudden Death in Relation to Aortic Stenosis, Am. Heart J. **10**:705, 1935.

5. Contratto, A. W., and Levine, S. A.: Aortic Stenosis with Special Reference to Angina Pectoris and Syncope, Ann. Int. Med. **10**:1636, 1937.

syncope for several years. One half of the group had less than six syncopal attacks, whereas the remainder had frequent episodes. Convulsions were noted in four patients, and two of these were injured during an attack.

The commonest electrocardiographic abnormality was a pattern of left ventricular strain. Auricular fibrillation and a first degree auriculoventricular block were each noted once. Only one patient had a normal electrocardiogram.

An associated aortic insufficiency was presented in 75 per cent of the 16 patients. If an aortic regurgitation is defined as physiologically significant when

TABLE 1.—*Patients with Syncope* *

Case No.	Age	No. of Attacks	Duration of Attacks, Min.	Yr. Since Onset of Attacks	Premonitory Symptoms	Ability to Abort Attack	Convulsions	Syncope Related to Effort	Angina	L.V.E.	Heart Weight, Gm.	A.I.	Blood Pressure	Electrocardiographic Results
1	47	Many	5 to 15	2	+	+	—	+	+	+	800	+	120/70	L.V.S.
2	56	3	—	14	—	—	—	+	0	+	...	+	154/92	Auricular fibrillation L.V.S.
3	58	Many	30 to 60	2	+	+	0	+	0	+	...	+	120/108	L.V.S.
4	70	2	—	1	—	—	—	+	+	+	...	+	112/94	L.B.B.B.
5	52	2	—	13	—	—	+	—	+	+	...	+	102/55	L.V.S.
6	54	1	—	8	—	—	—	—	+	+	...	+	126/78	L.V.S.
7	55	Many	30	5	—	—	0	+	+	+	610	+	92/80	L.V.S.
8	54	6	10 to 30	2	+	+	+	+	0	+	...	+	120/70	L.V.S.
9	45	Many	30 to 45	5	+	+	0	+	+	+	...	+	125/80	L.V.S.
10	32	Many	10 to 15	4	+	0	+	+	0	0	...	0	108/88	Inverted T_2 and T_3
11	57	3	—	2	+	0	—	+	+	+	...	0	120/96	Normal
12	67	3	—	2	—	—	—	+	+	+	...	+	145/110	1st degree A.V. block; L.V.S.
13	47	Many	5	20	—	—	0	+	+	+	...	+	120/68	R.B.B.B.
14	54	6	—	2	—	—	—	+	+	+	500	0	100/80	L.V.S.
15	54	Many	15 to 60	4	+	+	+	+	+	+	...	0	118/106	L.V.S.
16	54	Many	1 to 5	1	+	+	0	+	+	+	925	+	124/96	L.V.S.

* Key to symbols: — indicates no information available; +, symptom present; 0, absent; L.V.E., left ventricular enlargement; A.I., aortic insufficiency; A.V., auriculoventricular; L.V.S., left ventricular strain pattern; L.B.B.B. left bundle branch block, and R.B.B.B., right bundle branch block.

TABLE 2.—*Relation of Angina to Syncope*

	Total Patients	Patients with Angina	Per Cent
Syncope	16	12	75
Without syncope	47	11	23.4

associated with a pulse pressure over 50 mm. Hg or a diastolic pressure below 70 mm. Hg, then only 18.8 per cent of these patients had a significant aortic insufficiency. Mitral stenosis occurred in only one patient. Three of the four deaths were due to pulmonary edema. In the other patient the mode of death was sudden and unexplained.

COMPARISON OF PATIENTS WITH AND WITHOUT SYNCOPE

Angina occurred in 75 per cent of the patients with syncope but in only 23.4 per cent of the group without syncope (table 2). This represents a highly significant difference: χ^2 with Yates's correction = 11.57; $p = <0.01$. The only

other significant difference between the two groups was the incidence of left ventricular enlargement as demonstrated by roentgenograms or fluoroscopy (table 3). Left ventricular enlargement occurred in 93.8 per cent of the patients with syncope and 57.4 per cent of those without syncope (χ^2 with Yates's correction $= 5.54$; $p = <0.02$). There was no significant difference between the patients with and those without syncope as regards age, duration of heart disease, history of rheumatic fever, mortality, presence of heart failure, occurrence of aortic insufficiency or involvement of the mitral valve.

The average heart weight of four autopsied patients with syncope was 723.8 Gm., as compared with a weight of 586.6 Gm. for 19 patients without syncope. This difference was not statistically significant, probably because of the small number of autopsied patients ($t = 1.42$; $p = 0.2$ to 0.1).

OBSERVATIONS ON A PATIENT WITH AORTIC STENOSIS DURING SYNCOPE

One patient (case 10) was observed before and during a syncopal attack precipitated by effort. A continuous electrocardiogram and frequent determinations of the blood pressure and pulse rate were made. A control electrocardiogram showed negative T waves in leads II and III and 0.5 mm. depression of the S-T segment in lead II (fig. 1). The blood pressure was 108 mm. Hg systolic and 88 diastolic. The patient was exercised for three minutes by stepping up and down an

TABLE 3.—*Relation of Left Ventricular Enlargement to Syncope*

	Total Patients	Patients with L.V.E.	Per Cent
Syncope	16	15	93.8
Without syncope	47	27	57.4

18 inch (46 cm.) platform at the rate of one step every two seconds. He felt weak and appeared pale but was able to lie down with assistance. While the patient was still conscious, the T wave in lead II became upright and the S-T segment depressed to 2.4 mm., but the rate and rhythm were unchanged (fig. 2*A*). Although syncope then ensued, the electrocardiogram showed no further change except for a slight decrease in heart rate (fig. 2*B*). About 50 seconds after the loss of consciousness, the heart rate slowed from 68 per minute to 40 and generalized convulsions occurred. Radial and femoral pulsations were absent, and the blood pressure could not be obtained. Apnea was present for 10 to 20 seconds. During this period heart sounds could not be heard, although ventricular complexes were visible on the electrocardiogram. The heart rate slowed further, with the appearance of a sinoauricular block and nodal escape (fig. 2*C*). Later a sinus rhythm reappeared, followed by sinus tachycardia (fig. 2*D*). Six minutes after the onset of syncope the blood pressure was again obtainable and was 90 mm. Hg systolic and 65 diastolic. The arterial tension increased to 200 mm. Hg systolic and 100 diastolic. After 12 minutes, consciousness was restored and the arterial tension was 130 mm. Hg systolic and 90 diastolic. Ventricular complexes were visible on the electrocardiogram throughout the entire attack. The maximum S-T depression in lead II was 3 mm. Immediately after the attack the electrocardiogram resembled the control record.

COMMENT

The syndrome of effort syncope is so characteristic that one may be led to suspect aortic stenosis from the history alone. This relation to effort, previously stressed by Gallavardin[2] and Gravier,[3] is relatively unique. The association of convulsions with this form of syncope is not generally appreciated. The disorder in two of the patients in this series was erroneously diagnosed as idiopathic epilepsy by members of the neurological service.

The incidence of syncope in the present patients is higher than in most series.[6] The criteria used in the selection of these patients would tend to exclude those with mild degrees of aortic stenosis. The production of syncope is not dependent on the presence of aortic insufficiency. Syncope was noted in patients without

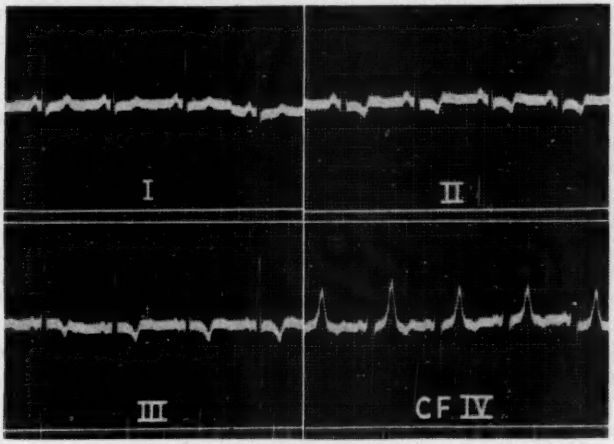

Fig. 1—Control electrocardiogram.

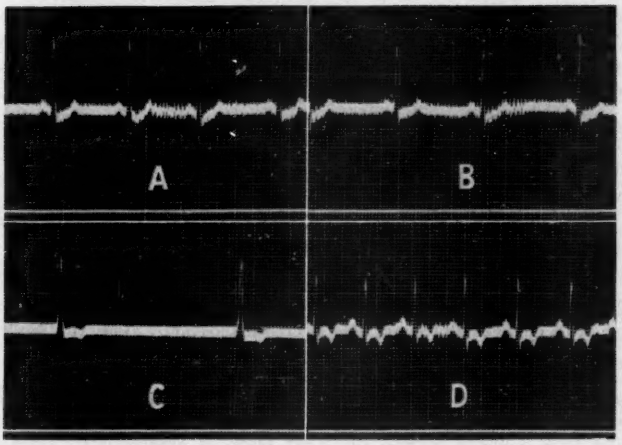

Fig. 2.—*A*, lead II after exercise but before syncope. *B*, lead II immediately after loss of consciousness. *C*, lead II after two minutes of syncope. *D*, lead III after five minutes of syncope.

6. (*a*) Contratto and Levine.[5] (*b*) Kumpe, C. W., and Bean, W. B.: Aortic Stenosis: A Study of the Clinical and Pathologic Aspects of 107 Proved Cases, Medicine **27**:139, 1948; (*c*) Dry, T., and Willius, F.: Calcareous Disease of the Aortic Valve, Am. Heart J. **17**:138, 1939.

aortic regurgitation and in patients with physiologically insignificant aortic insufficiency.

Various mechanisms for the production of syncope have been proposed. These include a hyperactive carotid sinus,[4] vascular disease of the brain,[6b] ventricular standstill, ventricular tachycardia, complete heart block and reduced cardiac output.[7] Occasionally, patients with aortic stenosis may have complete heart block due to involvement of the auriculoventricular conduction system[8] by calcification or fibrosis. One such patient with syncope has been described.[9] Syncope related to complete heart block, so-called Stokes-Adams syndrome, is not, however, associated with effort. Hypersensitive carotid sinus syndrome is also dissimilar to the picture presented by patients with aortic stenosis. In addition, no one has demonstrated an increased incidence of hyperactive carotid sinuses in patients with aortic stenosis.[6a, b] There is no apparent reason to implicate vascular disease of the brain as the basis for the production of syncope. These explanations for the syncope of aortic stenosis are inadequate.

A review of the careful observations that have been made during syncope in patients with aortic stenosis could perhaps elucidate this problem. Gallavardin and Rougier in 1928[10] observed a patient with aortic stenosis during numerous syncopal attacks. Electrocardiograms were recorded during two episodes. The attacks occurred after effort. Angina was the first symptom, followed by pallor, syncope and convulsions. The arterial pulse disappeared at the onset of the attack and gradually returned during recovery. Heart sounds were diminished. The electrocardiogram showed only depressed S-T segments during the early phase of syncope. The heart rate and rhythm were unchanged, although arterial pulsation had disappeared. Later, sinoauricular block and nodal escape supervened. Ventricular activity continued throughout the attack.

Marvin and Sullivan[4] in 1935 made similar observations. The syncope was precipitated by exercise, but the electrocardiographic record was not begun until after the onset of syncope. A conspicuous depression of the S-T segments, a nodal rhythm and bradycardia were the first changes noted on the electrocardiogram. The arterial tension was reduced. Sinus rhythm was then restored and was followed by supraventricular tachycardia.

Gravier[3b] in 1936 precipitated six attacks in a patient with aortic stenosis. Angina occurred and was followed by dizziness or syncope. Examination during the attacks showed disappearance of the systolic thrill, a weak apical impulse, slowing of the pulse rate from 80 per minute to 60 and an absence of pulsations in the femoral arteries. Inversion of the T waves and slowing of the heart rate were the only changes noted on the electrocardiogram. The rhythm remained normal, and ventricular activity persisted throughout the attack.

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7. (*a*) Gravier.[3b] (*b*) Harrison, T. R.: Failure of the Circulation, ed. 2, Baltimore, Williams & Wilkins Company, 1939, p. 39.

8. Boas, E. P.: Angina Pectoris and Heart Block, as Symptoms of Calcareous Aortic Stenosis, Am. J. M. Sc. **190**:376, 1935. Cohen, L.; Gray, I.; Nash, P., and Fink, H.: Calcareous Aortic Stenosis: Report of 9 Cases with Autopsy Findings, Ann. Int. Med. **13**:2091, 1940.

9. Warshawsky, H., and Abramson, W.: Complete Heart Block in Calcareous Aortic Stenosis, Ann. Int. Med. **27**:1040, 1947.

10. This case report, with the electrocardiographic records, was first published in 1928 (Paris méd. **69**:15, 1928) as a description of a patient with angina pectoris and syncope. The presence of aortic stenosis was not recognized until later, when an autopsy was performed. The results of the autopsy were published in 1932 (Rev. méd. franç. **13**:339, 1932).

These observations and the findings in the case presented in this report indicate that syncope is not dependent on an abnormal cardiac rhythm, since in three instances unconsciousness occurred before the appearance of an arrhythmia. In the only instance in which a cardiac arrhythmia was one of the first observed changes, the observations were not begun until syncope was established. Once an arrhythmia occurs, it tends to prolong the cerebral ischemia. The arrhythmia is probably secondary to syncope and could be explained on a reflex basis.

The disappearance of arterial pulsations and reduced or absent blood pressure, with persistence of ventricular contractions, can be explained by either vasodilatation or reduced stroke volume. Disappearance of the systolic thrill, weak apical impulses and absent heart sounds suggest a reduced stroke volume. A sudden reduction in cardiac output could lead to cerebral hypoxia and eventually syncope. A reduced stroke volume could, presumably, result from ischemia of the left ventricular myocardium, as suggested by Harrison.[7b] Tennant and Wiggers [11] have shown in dogs that myocardial ischemia results in immediate weakening of contractions in the ischemic area. The depressed S-T segments and T wave changes which occurred in all four patients in whom electrocardiograms were recorded during syncope indicate that myocardial ischemia was present. Furthermore, certain features of the syncopal attacks suggest a relationship to myocardial ischemia. The precipitation by effort and the relief by rest are analogous to angina pectoris. The occurrence of angina before a syncopal attack and the significant incidence of angina in patients with syncope definitely indicate a relationship. Syncope occurs in patients with larger hearts, and a relative reduction in coronary blood flow would be expected. Studies of coronary blood flow in experimental aortic stenosis in dogs have given conflicting results, depending on the method used.[12] None of these experiments has duplicated chronic aortic stenosis. Theoretical considerations would suggest at least a relative reduction in coronary blood flow in aortic stenosis. The use of coronary sinus catheterization to determine coronary blood flow should furnish some exact information.

No efficacious therapy for syncope associated with aortic stenosis has been suggested. The methods used for the treatment of other forms of cardiac syncope do not have rational application in this instance. Fortunately, some of the patients have premonitory symptoms so that rest at the onset of an attack may prevent syncope, and restriction of activity may bring welcome relief from the alarming episodes.

SUMMARY

Syncope occurred in 16 of 63 patients with aortic stenosis. Syncope was commonly precipitated by effort and appeared to be related to the occurrence of angina. Observations on one patient during syncope are reported. Syncope occurred before a cardiac arrhythmia was established, and ventricular activity continued throughout the attack. A review of similar observations on three patients recorded in the literature suggests that the mechanism for syncope in aortic stenosis may be cerebral hypoxia due to reduced cardiac output. The possibility that this reduced output is related to myocardial ischemia rather than to cardiac arrhythmia is suggested.

11. Tennant, R., and Wiggers, C. J.: The Effect of Coronary Occlusion on Myocardial Contraction, Am. J. Physiol. **112**:351, 1935.

12. Gregg, D. C.: The Coronary Circulation, Physiol. Rev. **26**:28, 1946.

Case Reports

EOSINOPHILIC LEUKEMIA WITH REPORT OF A CASE

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EOSINOPHILIC leukemia or so-called myeloid leukemia with pronounced eosinophilic predominance is an extremely rare disorder. A review of the literature reveals considerable hesitancy to admit its existence as a distinct clinical entity. Its separate identity has been questioned in the reported cases because of the relative maturity of eosinophils in the peripheral blood and bone marrow, as contrasted with the large numbers of immature cells observed in the more familiar forms of leukemia. As a further difficulty, in chronic myeloid leukemia especially, there is often a relative increase in eosinophils, both mature and immature. Traditionally, there has been slowness to accept other forms of leukemia when first described. The existence of monocytic leukemia is still denied by some observers.

In 1912 Stillman [1] presented the first case of myeloid leukemia with predominance of eosinophilic cells. Since then, approximately 25 similar cases have been described in the form of single case reports. The earlier workers considered their cases to be examples of myeloid leukemia with eosinophilic proliferation, whereas later authors seemed to favor the entity of eosinophilic leukemia. Evans and Nesbit,[2] in an excellent article, have recently reviewed the literature.

The following case meets the criteria for eosinophilic leukemia. It is unique in showing the equally rare complication of leukemia cutis. Therapy with nitrogen mustard (methyl-*bis*[beta-chloroethyl]amine hydrochloride and *tris*[beta-chloroethyl]amine hydrochloride) and urethan was also attempted for the first recorded time in this type of leukemia.

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1. Stillman, R. G.: Myeloid Leukemia with Predominance of Eosinophilic Cells, Med. Rec. **81**:594, 1912.

2. Evans, T. S., and Nesbit, R. R.: Eosinophilic Leukemia: Report of Case with Autopsy Confirmation; Review of Literature, Blood **4**:603, 1949.

REPORT OF CASE

This 24 year old white man was first admitted to the hospital in July 1948, complaining of easy fatigability for one year, a lump in the left groin for four months and similar masses in the right cervical and right inguinal regions for two weeks. He appeared chronically ill and moderately anemic. The spleen and liver were both enlarged to 3 fingerbreadths below the costal margins. There were a 3 by 4 cm. egg-shaped, firm, discrete mass in the right femoral region and walnut-sized nodes in the left inguinal area. Moderate cervical adenopathy was present. Red blood cells numbered 4,300,000, with 12.5 Gm. of hemoglobin. The total white blood cell count was 15,000, with 69 per cent eosinophils, 20 per cent polymorphonuclear forms and 11 per cent lymphocytes. The eosinophils were all of the mature variety, with two or three lobes to the nuclei. Numerous complete blood counts showed an eosinophilia, the count varying between 40 and 75 per cent, with white blood cell counts ranging from 15,000 to 30,000 and differential counts similar to that made on admission. Thrombocytes (platelets) varied from 88,000 to 250,000. The blood Kahn reaction was negative, and urinalyses showed no abnormality. Sternal marrow aspirations revealed a great proliferation of granulocytes, with cells in all stages of development. Myelocytic cells were numerous, with good maturation to segmented cells. A large percentage of myelocytes and segmented cells was eosinophilic. Biopsy of a lymph node showed primitive, nongranular cell proliferation interpreted as myeloblastic invasion. A diagnosis of eosinophilic leukemia was made on the basis of the peripheral blood and bone marrow showing eosinophilic proliferation, plus the hepatosplenomegaly and generalized lymphadenopathy. A course of therapy with nitrogen mustard (10 mg. daily for four days) was given in August 1948, followed by an immediate reduction in size of the spleen and lymph nodes. The white blood cell count dropped to 10,000, but eosinophilia (75 per cent) persisted. The patient showed improvement both subjectively and objectively. On examination six weeks later he continued to feel well but again noted increasing adenopathy of the cervical and inguinal regions. The spleen and liver were again found to be enlarged, and a repeat lymph node biopsy showed leukemic infiltration with large numbers of blast cells. He was given another course of treatment with nitrogen mustard in October 1948, followed again by regression in the size of the spleen and lymph nodes. The white blood cell count decreased from 27,000 to 6,000, but there was no definite change in the differential count. The patient was discharged in October 1948, and therapy with liver, iron and vitamin preparations was to be continued.

He was again seen in January 1949 as an outpatient, at which time his general condition appeared good and the blood picture was unchanged. He was readmitted in February 1949 because of tender adenopathy of the cervical and inguinal regions. Results of sternal marrow biopsy were again reported as consistent with a diagnosis of eosinophilic leukemia. Most of the stab and juvenile forms were eosinophils. Because of severe nausea and vomiting following previous nitrogen mustard therapy, he was given urethan U. S. P. (2 Gm. twice daily) from Feb. 8 to Feb. 19, 1949, when the dosage was reduced to 0.5 Gm. twice daily. Cervical and inguinal nodes became nontender and much smaller, and the spleen decreased in size but remained palpable. Again the total white blood cell count dropped to normal, although the eosinophilia remained unchanged. He was discharged and was to continue to take urethan in the amount of 2 Gm. daily as a maintenance dose. He was followed monthly on an outpatient basis with similar blood counts, until his final admission in July 1949.

At this time the patient noted a recurrence of the mass in the right groin, but his general condition was otherwise quite good. The appearance on the third sternal marrow aspiration was consistent with the diagnosis of eosinophilic leukemia. Roentgen therapy was decided on because of the localized, orange-sized right femoral mass and further enlargement of the spleen. He received three treatments to the spleen (350 r) and three to the right femoral region (920 r). There was no change in the white blood cell counts, but a good shrinkage of the nodes and spleen was obtained. While receiving roentgen therapy, he displayed a macular, erythematous rash over the trunk, which later spread to the extremities. These lesions gradually became raised and infiltrated; eventually some became hemorrhagic. A skin biopsy specimen revealed infiltration with mononuclear cells. Some were recognizable as myelocytes, but the majority had round to oval nuclei with dense, finely divided chromatin and single nucleoli. The cytoplasm was scanty, pale eosinophilic material. The histological diagnosis was leukemia cutis. At the same time, a septic elevation in temperature developed, with numerous ulcers of the oropharynx,

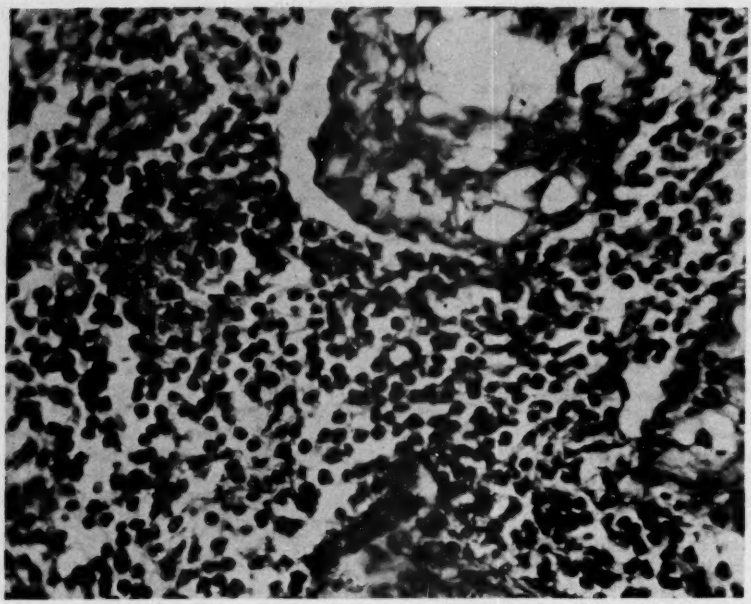

Fig. 1.—Section of testis showing diffuse interstitial infiltration by primitive myeloid cells. There is severe atrophy of the spermatogenic cells of the tubules. Hematoxylin and eosin stain; × 400.

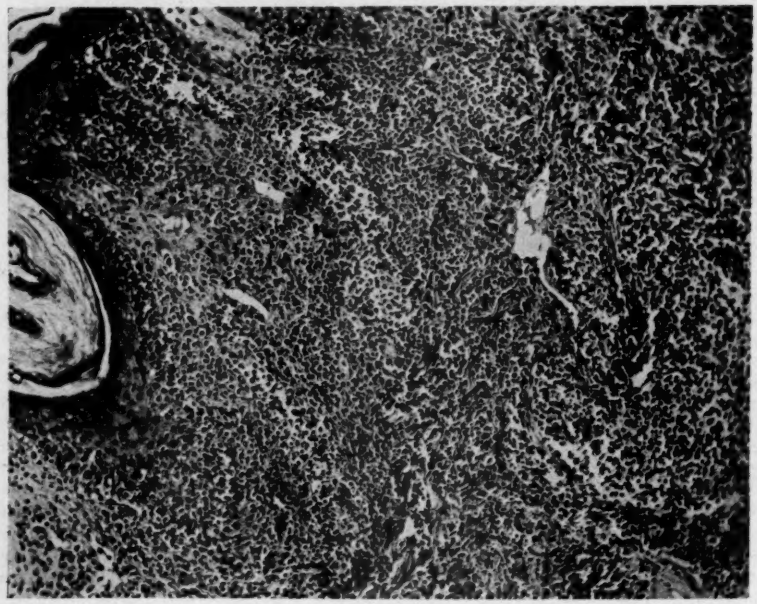

Fig. 2.—Section of skin of wall of chest showing diffuse infiltration of corium by myeloid cells. (See fig. 3.) Hematoxylin and eosin stain; × 110.

especially over the right lingual tonsil, which was greatly enlarged. Blood counts revealed no change, except for increasing anemia, for which the patient received numerous blood transfusions. All lymph nodes rapidly enlarged, and ankle edema developed, progressing to moderate anasarca, although the serum proteins remained normal. Treatment with nitrogen mustard was again tried, but after two doses the patient rapidly showed leukopenia, with white blood cells ranging from 1,000 to 2,000, polymorphonuclear forms from 12 to 28 per cent, lymphocytes from 32 to 44 per cent and eosinophils from 36 to 52 per cent, with occasional basophils. The skin lesions regressed considerably after the second dose of nitrogen mustard; they rapidly became flat and began to fade. However, the patient's general condition continued to decline. The mucous membrane ulcerations spread throughout the mouth, causing severe pain and discomfort. Transfusions maintained the hemoglobin concentration, but he gradually became weaker and died two months after his final admission (17 days after the final course of nitrogen mustard therapy).

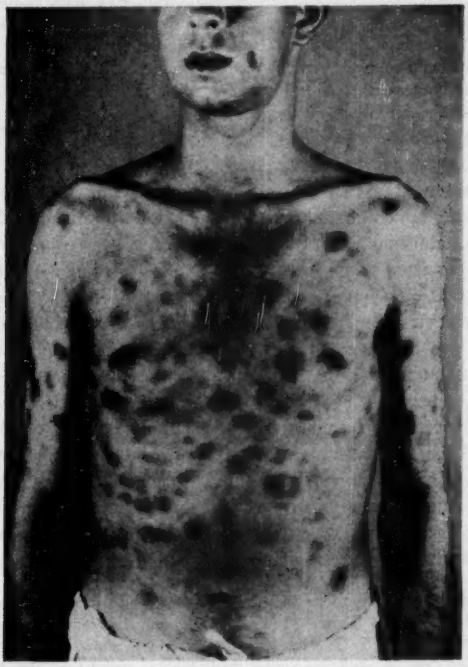

Fig. 3.—Photograph of trunk and upper extremities showing skin manifestation of leukemia cutis. The biopsy specimen of the skin was taken from the wall of the chest.

Autopsy Observations.—Gross Study: There was a generalized, macular, brown to purple rash, mostly discrete, but with areas of confluence measuring up to 4.5 cm. The lungs showed firm, dark blue-black areas in the lower lobes, which on cut surface were dark red and bulging. The liver weighed 3,375 Gm. and on cut surface was variegated red-brown and gray. It had a granular feel on cutting and to palpation. Splenic weight was 1,500 Gm., and the cut surface was dark red, bulging and friable and felt coarsely granular. Multiple scattered, slightly raised nodular lesions, many of which were ulcerated and hemorrhagic, were seen throughout the stomach and intestine. Hemorrhagic areas were also seen in the adrenal glands and testes bilaterally. Massive lymph node enlargement was present in the peribronchial, posterior medi-

astinal, mesenteric, para-aortic and iliac regions. These were hard and discrete with pale yellow, patchy, hemorrhagic cut surfaces. The largest measured 7.5 by 4.5 by 3 cm.

Microscopic Study: Sections of the lungs showed patchy consolidation; the alveoli were filled with polymorphonuclear forms and red cells. Small, necrotic areas filled with bacteria were also present. The liver showed a normal lobular architecture, but there were intense congestion, histiocytic proliferation and erythrophagocytosis in the sinusoids. Normal splenic architecture was destroyed by massive engorgement with red cells. Erythrophagocytosis was widespread, and several patches of leukemic infiltration were observed. The predominant cell was large and primitive, with a large deeply staining round nucleus and a very thin rim of cytoplasm. Nucleoli were made out in some cells. The ulcers of the stomach, ileum and colon were of the necrotic, hemorrhagic type. Many fat-laden histiocytes and lymphocytes were present in the submucosa, and leukemic infiltration with blastic cells was found in the lamina propria of the stomach and colon. A loose infiltration of blastic cells throughout the adrenal glands was noted, but the most notable leukemic picture was seen in the testes, where primitive myeloblastic cells were numerous, with complete atrophy of the seminiferous tubules. Myeloblastic cells were seen infiltrating the lymph nodes, with destruction of normal architecture. Bone marrow preparations were, unfortunately, unsatisfactory for study.

COMMENT

We have presented a case of eosinophilic leukemia in a young man whose total illness lasted approximately two years and who lived 14 months after a diagnosis was established. Peripheral eosinophilia, the counts ranging from 33 to 79 per cent, persisted throughout the course, with total white blood cell counts of 6,000 to 35,000. In only three of over 60 differential smears were single eosinophilic myelocytes seen. The remainder of the eosinophils were of the mature variety, having two or three lobed nuclei. Neutrophils ranged from 8 to 48 per cent, with normal numbers of band forms but no myelocytes. Basophils were present up to 4 per cent. Other investigators [3] have described characteristic morphological aspects of the circulating eosinophils in this condition. They are generally said to be somewhat larger than normal with slightly basophilic, sometimes vacuolated, cytoplasm. There tends to be a decrease in the number of eosinophilic granules, which may be larger than normal and heaped into one section of cytoplasm. In 15 cases of chronic eosinophilic leukemia reviewed,[4] 10 showed only mature two or three lobed eosinophils in the peripheral blood, and

3. (*a*) Stillman.[1] (*b*) Thomsen, S., and Plum, P.: Eosinophilic Leukemia, Acta med. Scandinav. **101**:116, 1939. (*c*) Shapiro, L. G.: Eosinophilic Leukemia: Report of a Case, Proc. New York Path. Soc. **19**:73, 1919. (*d*) McDonald, S., and Shaw, A.: Persistent Eosinophilia with Splenomegaly, Brit. M. J. **2**:966, 1922. (*e*) Hay, J., and Evans, W.: Acute Eosinophilic Leukemia and Eosinophilic Erythroleukemia, Quart. J. Med. **22**:167, 1929. (*f*) Fenner, F.: A Case of Eosinophilic Leukemia, M. J. Australia **2**:7, 1943. (*g*) Stephens, D. J.: Acute Eosinophilic Leukemia, Am. J. M. Sc. **189**:387, 1935.

4. (*a*) Stillman.[1] (*b*) Footnote 3*b* to *f*. (*c*) Giffin, H.: Persistent Eosinophilia with Hyperleukocytosis and Splenomegaly, Am. J. M. Sc. **158**:618, 1919. (*d*) Alexander, M. E.: Observations on a Case of Splenomegaly with Hyperleukocytosis, J. Lab. & Clin. Med. **9**:803, 1924. (*e*) Harrison, F. F.: Eosinophilia with Splenomegaly, Am. J. M. Sc. **170**:208, 1930. (*f*) Friedman, M.; Wolman, I. J., and Tyner, H. H.: Eosinophilic Leukemia, with Report of a Case, ibid. **208**:333, 1944. (*g*) Goehl, R.: Eosinophilic Leukemia with a Case Report, Journal Lancet **62**:252, 1942. (*h*) Hodgson, J. R.; Kaump, D. H.; Steiner, G., and Bovill, J.: Myeloid Leukemia, Probably Eosinophilic in Character, Am. J. Clin. Path. **15**:309, 1945. (*i*) Drennan, A. M., and Biggart, J. H.: Persistent Eosinophilia, J. Path. & Bact. **33**:995, 1930. (*j*) Ravault, P.; Girard, M., and Revol, L.: La leukémie aiguë à éosinophiles, Sang **16**:258, 1944. (*k*) Gloetzner, H. J., and Marx, H. E.: Eosinophilic Leukemia, Delaware State M. J. **19**:12, 1947.

this was the predominant cell in the remaining five. Comparison of our slides with those from cases of peripheral eosinophilia due to other causes demonstrated no definite consistent morphological differences.

Because of moderate leukocytosis, the diagnosis of leukemia was somewhat in doubt early in the study. However, the lymph node biopsy specimen showing leukemic infiltration, the hepatosplenomegaly, generalized lymphadenopathy and bone marrow studies disclosing advanced eosinophilic proliferation were all compatible with observations in previously reported cases of eosinophilic leukemia. Some of these demonstrated a moderate, and others an enormous, leukocytosis, which was always found to be due mainly to an absolute increase in eosinophils in contrast to only a small increase in neutrophils. In the few cases with bone marrow studies [5] there was proliferation of the entire eosinophilic series, as was

Results of Bone Marrow Studies

Cells	Cells per 100 Cells			
	August 1948	February 1949	July 1949	Normal
Hemocytoblasts	4.0	0	1.3	1 to 2
Promyelocytes	0.5	1.0	1.0	4 to 8
Myelocytes	32.0	9.6	24.9	10 to 20
Neutrophilic	22.0	6.3	10.3	12
Eosinophilic	10.0 *	3.3 *	14.6 *	1.5
Juvenile forms	13.5	5.0	11.6	....
Neutrophilic	7.0	1.6	7.0	20 to 25
Eosinophilic	6.5 *	3.4 *	4.6 *	....
Stab cells	8.0	6.0	17.3	....
Neutrophilic	2.0	1.0	10.0	5 to 10
Eosinophilic	6.0 *	5.0 *	7.3 *	....
Segmented forms	17.5	61.9	19.3	22
Neutrophilic	11.5	15.3	1.3	20
Eosinophilic	6.0 *	46.6 *	18.0 *	2
Erythroblasts	2.5	0	4.0	2 to 4
Normoblasts	22.0	3.3	11.7	22 to 35
Lymphocytes	0	12.3	7.3	10 to 20
Monocytes	0	0.3	0	1 to 5
Smudge forms	0	0	1.6	....

* Asterisks call attention to the unusual eosinophilic counts.

noted in our patient (table). But, as in the peripheral blood, the bone marrow generally falls far short of the degree of immaturity found in the usual case of myelogenous leukemia. Other constant findings in the chronic disease have been enlarged liver, spleen and lymph nodes. Cases of the acute condition show large numbers of primitive cells in the peripheral blood.[6]

The sudden appearance of leukemia cutis during roentgen therapy was startling, as it was exactly at this time that the violent septic, downhill course began.

5. Evans and Nesbit.[2] Thomsen and Plum.[3b] Fenner.[3f] Friedman and others.[4f]

6. Evans and Nesbit.[2] Footnote 3*e* and *g*. Forkner, C.; Teng. C. T.; Ch'U. Y. C., and Cochran, W.: Eosinophilocytic or Eosinophilic Myelogenous Leukemia, Chinese M. J. **51**:609, 1937. McCowen, G. R.; Parker, H. B., and Panton, P. N.: A Case of Acute Eosinophilic Leukaemia, J. Roy. Nav. M. Serv. **18**:131, 1932. Bass, M. H.: Unusual Eosinophilia with Splenomegaly (Eosinophilic Leukemia?) in Child Aged 6 Years, Am. J. M. Sc. **170**:416, 1925. Gray, J. D., and Shay, S.: Eosinophilic Leukemia and Familial Eosinophilia, Lancet **2**:1131, 1949.

The cellular infiltration of the skin was similar to that seen at autopsy in all other organs. Some of the cells were recognizable as myelocytes, but most were the same large primitive mononuclear cells with round to oval nuclei, having a single nucleolus. A few eosinophils were seen, but all were in or near blood vessels. It was the pathologist's opinion that the infiltrations in the skin and viscera at autopsy were compatible with an acute leukemic process, or at least an acute exacerbation of a chronic process. We are unable to explain this incompatibility between the morphological maturity of the peripheral blood and the primitive leukemic infiltration seen at autopsy. It is entirely possible that these blastic cells were precursors of the eosinophils, although it seems strange that not one of the blastic cells found its way into the blood stream.

Eosinophilia associated with Hodgkin's disease was reviewed in a case reported by Stewart[7] in 1929. A blood picture similar to that of eosinophilic leukemia was present, but at autopsy the histological picture was typical of Hodgkin's granuloma. In our case, no cells of the Reed-Sternberg type were seen, nor were fibrosis or other characteristics of Hodgkin's disease in evidence. Stewart's patient was an asthmatic with a strong family history of allergy and eosinophilia in three generations. There was no allergic background in our patient, and all other studies directed at establishing a causation for his eosinophilia were noncontributory.

It is problematic whether treatment with the newer chemotherapeutic agents, nitrogen mustard and urethan, prolonged the patient's life. Before each course of nitrogen mustard therapy he appeared seriously ill. Immediately afterward, his condition was improved clinically, although the blood picture was essentially unchanged, except for an improvement in the anemia. The two remissions with nitrogen mustard treatment lasted only six weeks, but an excellent and prolonged remission was achieved with urethan. During these six months he was able to work and felt relatively well while receiving a maintenance dose of 2 Gm. daily. Emphasis should be placed on the fact that the patient was critically ill before receiving his final course of treatment with nitrogen mustard, which precipitated the leukopenic reaction. Whether a relationship existed between the roentgen therapy and the final exacerbation remains, of course, purely in the realm of speculation.

CONCLUSIONS

A case of eosinophilic leukemia is presented and the syndrome reviewed. We believe this to be a rare but distinct entity.

Skin lesions, which on biopsy proved to be leukemia cutis, are described for the first time in this condition. It is felt that this further establishes the leukemic nature of the syndrome.

Therapy with nitrogen mustard and urethan was also attempted for the first time to the best of our knowledge; benefit was definite, but temporary.

Autopsy proved the leukemic nature of the disease.

Dr. William J. Winter, Assistant Chief Pathologist, Veterans Administration Hospital, Aspinwall, Pa., assisted in preparation of pathological material.

7. Stewart, S. G.: Eosinophilic Hyperleukocytosis in Hodgkin's Disease with Familial Eosinophilic Diathesis: Report of Case and Review of Literature, Arch. Int. Med. **44**:772 (Nov.) 1929.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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DURING the period covered by this fifteenth annual review of syphilis,[1] July 1, 1949 to July 1, 1950, the reviewers have been impressed with the rather unspectacular character of the material available for analysis. However, a few items are worthy of emphasis. Chief among these are the studies of Delamater and his co-workers at the University of Pennsylvania, dealing with the possible life cycle of Treponema pallidum, an effort which, even in its early stages, shows great promise. Also, Scott's investigation of the use of hyaluronidase for syphilis is perhaps the most novel of recent applications of a general principle of bacteriology to syphilology.

Most of the other work on experimental syphilis concerns penicillin, although there is still active interest in serology, in the cardiolipin antigen, the spirochetal immobilization test and a projected serologic conference. In clinical diagnosis of syphilis angiocardiography has been established as a valuable tool in the detection of syphilitic aortitis. The proper treatment of syphilis is not yet settled, but Mahoney and his group have shown the lasting effect of treatment in a five year follow-up study of the four original penicillin-treated patients.

In the case of syphilis in pregnancy and congenital syphilis there is almost universal agreement concerning principles of good practice. We have the definite feeling that reactions to penicillin are more frequently met with now. Some of these reactions are severe and even fatal. New drugs have also been introduced because of their antitreponemal activity, terramycin and chloramphenicol, and the value of aureomycin has been better established.

Among the readily accessible compilations of various aspects of syphilis which have appeared during the period covered by this review are World Health Organization Technical Report Series, No. 15, dealing with the report of the World Health Organization Syphilis Study Commission on venereal disease control in the

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Drs. Reynolds and Guthe are with the World Health Organization.

From the University of Pennsylvania, Departments of Dermatology and Syphilology, School of Medicine, Donald M. Pillsbury, M. D., Professor; the Graduate School of Medicine, Herman Beerman, M.D., Chairman, and the Institute for the Study of Venereal Disease, John H. Stokes, M. D., Director.

1. For reference to previous reviews, see Beerman, H.; Nicholas, L.; Buerk, M. S., and Ford, W. T.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **85**:305-358 (Feb.); 496-541 (March); 699-721 (April); 819-886 (May) 1950.

United States[2]; a revised edition of Moore's text[3]; "A Symposium on Current Progress in the Study of Venereal Diseases,"[4] sponsored jointly by the Syphilis Study Section of the United States Public Health Service and the American Venereal Disease Association; "Manual of Serologic Tests for Syphilis,"[5] and Moore's article "Recent Advances in the Study of Venereal Diseases."[6]

In his excellent review Moore[6] covers both the laboratory and the therapeutic aspects. He describes the recent studies on multiplication time of virulent T. pallidum in vivo, its cultivation on artificial mediums and its immobilization by antibody produced in syphilitic infection. Typical curves of serologic response in penicillin-treated syphilis are reproduced. Discussion of recent advances in therapy are included in sections on early abortive therapy, retreatment of pregnant women and treatment of cardiovascular syphilis and neurosyphilis—reports concerning all of which appear elsewhere in this review or in the review published in 1950.[1]

HISTORY OF SYPHILIS

The story of syphilis still holds the attention of the medical public. During the period of this survey discussions on the origin of syphilis and the history of the chancre and the reminiscences of two English venereologists of vast experience comprise the essential contributions in this field.

European Origin of Syphilis.—The view is still widely held that syphilis was introduced into Europe from the West Indies by members of Columbus' crews and that it first appeared in Barcelona in 1493. This has been stated without qualification by certan writers of these times, particularly Fernández de Oviedo and Ruy Díaz de Isla. According to Zapuente Mateos,[7] these authors produce no adequate evidence for their assertions. It is known that syphilis had assumed epidemic proportions by 1495, and Zapuente Mateos doubts that the disease could have become so widely disseminated in two years. Other evidence which he considers to indicate the existence of syphilis outside the Western Hemisphere prior to 1492 include (1) signs of osseous syphilis in skeletons found in pre-Columbian Europe; (2) literary references to syphilis from China (2637 B.C.), ancient Rome (Horace, *Satires,* V) and elsewhere; (3) the frequent use of mercury in the twelfth century for certain malignant skin diseases known as scabies grossa, variola grossa and scabies mala, which may have been syphilis, and (4) the descriptions of characteristic lesions by Guy de Chauliac in the fourteenth century.

History of the Word Chancre.—Keil[8] in a scholarly and well documented paper presents the evolution of the word chancre and its relation to the history of syphilis. The word was derived from the Latin word *cancer,* which was softened to-

2. Venereal Disease Control in the U. S. A., World Health Organization Technical Report Series No. 15, United Nations, World Health Organization, May 1950.

3. Moore, J. E.: The Diagnosis of Syphilis by the General Practitioner, J. Ven. Dis. Inform., 1949, supp. 23.

4. A Symposium on Current Progress in the Study of Venereal Diseases, Federal Security Agency, United States Public Health Service, Division of Venereal Disease, 1949.

5. Manual of Serologic Tests for Syphilis, J. Ven. Dis. Inform, 1949, supp. 22.

6. Moore, J. E.: Recent Advances in the Study of Venereal Diseases, Brit. J. Ven. Dis. **25**:169-178 (Dec.) 1949.

7. Zapuente Mateos, A.: Sífilis en Europa antes de 1492, Medicina, Madrid **18**:115-128 (Feb.) 1950.

8. Keil, H.: The Evolution of the Term Chancre and Its Relation to the History of Syphilis, J. Hist. Med. & Allied Sc. **4**:407-416 (Autumn) 1949.

chancre in Parisian dialect. The Latin word *cancer* was in turn a direct translation of the Greek καρκίνος, meaning crab. The uses of the words cancer, carcinoma, chancre and chancroid are traced from their origin.

Developments in the Treatment of Syphilis, 1899 to the Present.—The professional life of Harrison,[9] a pioneer in venereology, covers all the developments in knowledge of modern venereology (syphilology). In a fascinating address delivered before the Royal Medical Society, Edinburgh, in 1946, he outlines his personal contact with this important progress from "chaos to order."

General Historical Comments.—Osmond[10] surveyed venereal disease as it occurred before and during World War II. His material encompassed the problems which were tackled, difficulties encountered and success obtained. The military control measures employed and the pros and cons concerning brothels are discussed as fully as the various treatment schedules.

T. PALLIDUM AND OTHER TREPONEMES

The most outstanding work, in our opinion, in this year's contributions to the field of syphilology is that of the University of Pennsylvania group investigating the growth factors and possible life cycle of T. pallidum. Although this work is just beginning, the published material already indicates that with the concentrated effort now being expended the problem of the cultivation of pathogenic treponemes and the stages in their development may soon be an open book.

Cultivation of Nichols Test Tube and Kazan Strains of T. Pallidum.—In the first of the University of Pennsylvania studies Newcomer and Haanes[11] report the successful cultivation of the nonpathogenic Nichols test tube strain of T. pallidum in killed fertile hen's eggs. Five serial transfers from egg to egg have been accomplished for a total period of 81 days. Active treponemes of normal appearance have been observed by dark field examination of egg material at the time of each transfer. Positive subcultures in Bacto fluid thioglycollate medium have been observed in every instance in which eggs were dark field positive on direct examination. Growth of spirochetes in material from dark field–negative eggs was obtained by subculture in many instances. The authors are currently using the killed chick embryo as a medium in an effort to culture pathogenic T. pallidum.

In a later study DeLamater, Newcomer, Haanes and Wiggall[12] report initial studies on the life cycles of spirochetes, utilizing the phase contrast microscope. They compare this method with other means of observation and show that much greater detail may be seen. They present the details of their methods and also six photographs showing various developmental stages of the Nichols nonpathogenic spirochete. This work not only corroborates earlier isolated observations but offers a promising means for the further study of spirochetes, including T. pallidum.

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9. Harrison, L. W.: Half a Lifetime in the Management of Venereal Diseases, from Chaos to Order, Medicine Illus. **3**:318-324 (July); 376-385 (Aug.) 1949.

10. Osmond, T. E.: Venereal Disease in Peace and War, with Some Reminiscences of the Last 40 Years, Brit. J. Ven. Dis. **25**:101-114 (Sept.) 1949.

11. Newcomer, V. D., and Haanes, M.: Observations on the Growth of the Nonpathogenic Nichols Strain of Treponema Pallidum in the Embryonated Chick Egg Under Anaerobic Conditions, Am. J. Syph., Gonor. & Ven. Dis. **33**:318-322 (July) 1949.

12. DeLamater, E. D.; Newcomer, V. D.; Haanes, M., and Wiggall, R. H.: Studies on the Life Cycles of Spirochetes: I. The Use of Phase Contrast Microscopy, Am. J. Syph., Gonor. & Ven. Dis. **34**:122-125 (March) 1950.

In a third report Haanes, Wiggall and DeLamater [13] state that they have demonstrated the growth of the nonpathogenic Kazan strain of T. pallidum in the embryonated hen's egg maintained under anaerobic conditions. Ten and 15 day old eggs showed organisms on direct examination in 90.6 and 92.3 per cent, respectively, at the end of the two week incubation period. The morphological appearance of the organism when grown in the egg closely resembled that of pathogenic T. pallidum as it occurs in tissue. On subculture from the embryo to Brewer's thioglycollate medium the organisms were present predominantly as spirals and showed reproduction by transverse fission. Numerous unispirochetal cysts were present in the egg material, but only a few of the large cystic forms were observed. It was noted that 2 day old embryos did not support growth of the Kazan strain very well. There apparently was no difference between the yolk and the albumin as a site for inoculation. The morphological appearance of the Kazan strain of T. pallidum in eggs differed from that observed in Brewer's thioglycollate medium.

Rowe and Curtis [14] also attempted to culture T. pallidum in fertile hen's eggs which had been incubated at temperatures between 37 and 38 C. for six to 11 days prior to inoculation. Small pieces of testicular tissue from rabbits infected with the Nichols strain of T. pallidum were implanted on the chorioallantoic membranes of the eggs. The authors felt that their experiments did not demonstrate growth of T. pallidum in the fertile hen's eggs, since it has already been shown that the organism will remain motile in a saline suspension of infected rabbit testicular tissue at room temperature for up to 58 days. They concluded that the infectiousness of the egg material is probably due to the presence of spirochetes in the small pieces of tissue grafted onto the chorioallantoic membrane. Failure to demonstrate spirochetes in some of the infectious egg material was probably due to the small number of organisms present, and Magnuson has demonstrated that only one or two spirochetes are necessary to produce infection in the rabbit.

Culture of T. Pallidum.—Other studies in the field of cultivation of T. pallidum have also appeared during the review period. For example, Boak, Fawcett and Carpenter [15] observed motile spirochetes morphologically characteristic of T. pallidum in cultures from 21 testicular syphilomas in rabbits infected with six different strains of T. pallidum (Nichols, Ami, Fan, Est, Rei and Tho strains). Brewer's modified thioglycollate medium with 10 per cent inactivated goose or beef serum was employed.

Electron Microscope Studies of Treponemes.—Morton and Oskay,[16] from the University of Pennsylvania and the Squibb Institute of Medical Research, respectively, continued electron microscope studies of treponemes and observed the effects of penicillin on the Nichols strain. They reported that in the presence of subspirochetostatic concentrations of penicillin G in vitro there were a lengthening of

13. Haanes, M.; Wiggall, R. H., and DeLamater, E. D.: Observations on the Growth of the Nonpathogenic Kazan Strain of Treponema Pallidum in Embryonated Hens' Eggs of Various Ages, Am. J. Syph., Gonor. & Ven. Dis. **34**:214-218 (May) 1950.

14. Rowe, R. S., and Curtis, A. C.: Studies of the Life and Motility of Treponema Pallidum in Fertile Hens' Eggs, Am. J. Syph., Gonor. & Ven. Dis. **33**:303-307 (July) 1949.

15. Boak, R. H.; Fawcett, M. L., and Carpenter, C. M.: Studies on the Cultivation of Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **33**:409-415 (Sept.) 1949.

16. Morton, H. E., and Oskay, J.: Electron Microscope Studies of Treponemes: II. The Effect of Penicillin on the Nichols Strain of Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **34**:34-39 (Jan.) 1950.

individual cells, a tendency for incomplete fission so that chains of as many as six treponemes were observed and an occasional increase in transverse diameter of cells. Penicillin did not appear to suppress the flagella-like processes of the treponemes, nor were buds, lateral or terminal, or tightly coiled masses of treponemes observed.

EXPERIMENTAL SYPHILIS

Another worthy contribution to the syphilology of 1949-1950 is that of Scott and his co-workers, dealing with hyaluronidase in experimental syphilis. The results of this series of studies have definite clinical importance. Other contributions in the field of experimental syphilis continue along the lines of size of inoculum and various aspects of the disease in animals (serologic reactions and outcome of therapy). Although a number of the contributions in this field are intimately linked with chemotherapy, they are discussed here largely because the basic work is with animals. For the full picture, however, this section should be read in conjunction with the material presented later.

Role of Spreading Factor (Hyaluronidase).—Scott [17] calls attention to the role of spreading factor, chiefly testicular extracts, in experimental disease and immune processes. In a review of the literature he found no reports on the relation of spreading factor to experimental syphilis. He states that this seems to be an oversight, since in the study of syphilis in the experimental rabbit the testis (rich in spreading factor) is the usual site of inoculation, and the inoculum commonly employed is a saline suspension of ground testicular syphiloma. That this spreading factor is linked with spermatogenesis is indicated by the spreading activity of spermatozoa. Immature testes showed little or no activity; the maximum content of spreading factor in rat testis is achieved when testicular growth has reached its maximum. Physiological factors, including age, sex, constitutional states and individual and regional characteristics of the skin, have been found to be important elements in connective tissue permeability. Certain of the sex hormones have been shown to exert a modifying effect: The administration of estrogenic substances results in decreased connective tissue permeability; progestin and androgen have the opposite effect. It is generally agreed (Moore, Morgan and others) that syphilis is of greater severity in men than in women. In rabbits Chesney and Kemp and Shaw have shown that syphilis is likewise severer in males than in females. One possible explanation of the apparent sex difference is spreading factor, the male testis affording a rich source of this substance. In females there is the additional and opposing effect of the estrogens, injections of which experimentally result in decreased connective tissue permeability. Kemp and Shaw have shown that syphilis is milder in castrated than in normal males. Chesney and his co-workers demonstrated that granulating wounds on the skin of rabbits constitute a remarkably favorable site for the growth of T. pallidum. Chesney stated his belief that some factor elaborated by rapidly proliferating tissue favors the growth of T. pallidum. Scott also points out that the spreading factor may be in some way related to the development of interstitial keratitis. The age of onset, with the highest incidence at about puberty, suggests that a spreading factor, such as testicular extract, may be concerned. Meyer and Chaffee stated that they produced vascularization of the cornea with spreading factor derived from Pneumococcus filtrates but not

17. Scott, V.: Speculations on the Role of Spreading Factor (Hyaluronidase) in Experimental and Human Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:424-428 (Sept.) 1949.

with testicular extract. Scott concludes that the affinity of T. pallidum for certain tissues may be, at least in part, related to the type of ground substance and its permeability as affected by spreading factor.

In a second study Scott and Droegemueller [18] investigated the effect of the spreading factor on the incubation period of primary lesions in rabbits, following the inoculation of the animals via the intracutaneous route. The material used in the study was hyronase,* an extract of bull testes. The infectious inoculum was obtained from the popliteal lymph nodes of five rabbits. The duration of syphilis in these rabbits varied from six to 10 months. Thirty-four albino rabbits were inoculated intracutaneously with lymph node material plus hyaluronidase and lymph node material plus heat-inactivated hyaluronidase. The authors concluded that the results suggest that the addition of hyaluronidase effects a shortening of the incubation period.

Scott [19] also tried to produce localization of lesions in the skin and in the cornea by the intradermal and intracorneal injection of hyaluronidase into rabbits with active syphilitic infection. Localization of lesions in the skin of the back was not produced in 13 rabbits with syphilis of varying duration by the intradermal injection of 0.01 to 200 turbidity-reducing units (T.R.U.) of hyaluronidase. In 12 rabbits with syphilis of varying duration the intracorneal injection of hyaluronidase in large amounts (50 T.R.U.) was not followed by the development of syphilitic interstitial keratitis. The intradermal injection of hyaluronidase in amounts of 10 and 5 T.R.U. performed 28 hours, nine hours and one hour prior to intravenous inoculation of T. pallidum did not result in an apparent selective localization of syphilitic lesions in these sites.

In this same field Hussey and Nowinski [20] investigated the relation between T. pallidum and animal tissues. Heart, spleen, kidney, brain, small intestine and liver were cultured in vitro with the nonpathogenic Reiter strain of T. pallidum. The organisms appeared to invade the intercellular areas, loosening the cement substance. This fact suggested that the strain possesses hyaluronidase activity. Viscosimetric measurements fully confirmed the preliminary observations.

Factors Influencing the Course of Experimental Syphilis in the Rabbit and Mouse.—Method of Inoculation (Rabbit): Chesney and Schipper [21] report their observations on the course of experimental syphilis in rabbits, using three routes, intracutaneous, intratesticular and intravenous, for inoculation of the animals. The inoculum consisted of 0.1 cc. of an emulsion, in isotonic sodium chloride solution, of a portion of the testis of a syphilitic rabbit. It contained approximately 770,000 T. pallidum. Three groups of adult rabbits, all belonging to the Chinchilla breed, were inoculated with equal amounts of the Nichols strain of T. pallidum.

18. Scott, V., and Droegemueller, C.: Hyaluronidase and Experimental Syphilis: I. The Length of Incubation Periods in Experimental Primary Syphilis With and Without Hyaluronidase, Am. J. Syph., Gonor. & Ven. Dis. **34**:1-11 (Jan.) 1950.

19. Scott, V.: Hyaluronidase and Experimental Syphilis: II. The Attempted Localization of Lesions in Syphilitic Rabbits by Intradermal and by Intracorneal Injections of Hyaluronidase, Am. J. Syph., Gonor. & Ven. Dis. **34**:12-17 (Jan.) 1950.

20. Hussey, M. S., and Nowinski, W. W.: Hyaluronidase Activity in the Reiter Strain of Treponema Pallidum, Texas Rep. Biol. & Med. **7**:73-79 (Spring) 1949.

21. Chesney, A. M., and Schipper, G. J.: The Effect of the Method of Inoculation upon the Course of Experimental Syphilis in the Rabbit, Am. J. Syph., Gonor. & Ven. Dis. **34**:18-24 (Jan.) 1950.

One group of females was inoculated intracutaneously, another group of females intravenously and a third group of males intratesticularly. The course of the infection was observed for 85 days, by which time all lesions, both local and generalized, had healed, and no new ones had appeared.

Size of Inoculum (Rabbit): Wiggall and Chesney [22] present detailed observations on the effect of the size of the inoculum on the course of syphilis in the rabbit. Two groups of female rabbits of the same breed (Chinchilla) were divided so that each corresponded closely to the other with regard to weight (and age) and were inoculated intravenously with different amounts of T. pallidum. One group received 770,000 treponemes, the other 7,700. In the 45 animals receiving the larger inoculum, 39 (87 per cent) had lesions recognizable by inspection or palpation, whereas among 42 animals receiving the smaller inoculum lesions were observed in 20, or 48 per cent. The total number of lesions of any sort developing in animals receiving the larger inoculum was 232, as against 148 in the animals receiving the smaller inoculum. The total number of animals proved to have been infected (lymph node transfers were done on all negative animals) with the larger inoculum was 43 of 45 inoculated, whereas the total number proved to have been infected with the smaller inoculum was 33 of 42. The incidence of asymptomatic infections was 40 per cent in the animals receiving the smaller inoculum, as against 9.3 per cent in the animals given the larger inoculum. In the animals in which an asymptomatic infection developed, the lymph nodes were found to be infectious more frequently than the liver, indicating that they are a more constant reservoir of syphilitic infection than that organ. The authors conclude that when injected intravenously the number of organisms has a direct effect on the course of syphilis in the rabbit, although they mention other factors which must be considered.

Method of Inoculation and Serologic Outcome (Rabbit): Schipper and Chesney [23] studied the serologic response in three groups of rabbits inoculated by three routes, intracutaneous, intratesticular and intravenous. Reactions to three standard serologic tests employed in the study followed the same general pattern, reaching their maximum degree of positivity about the eighteenth day after inoculation and declining to a low titer after that time. The authors conclude that the method of inoculation exerts a considerable effect on the course of experimental syphilis in the rabbit. They suggest that the syphilitic inflammatory lesion which develops in the skin at the site of the intracutaneous inoculation may have a partially immunizing effect and, thus, may suppress to some extent the development of generalized lesions in the infected animal, and that the high incidence of such lesions after intravenous inoculation may be due to a greater number of infecting organisms in the circulating blood.

Size of Inoculum (Mouse): Rosahn and Rowe [24] inoculated mice intraperitoneally with graded dilutions of T. pallidum varying from 25,000 to 5,000,000 organisms.

22. Wiggall, R. H., and Chesney, A. M.: The Effect of the Size of the Inoculum (Number of Treponemes) upon the Course of Experimental Syphilis in the Rabbitt, Bull. Johns Hopkins Hosp. **86**:191-199 (April) 1950.

23. Schipper, G. J., and Chesney, A. M.: The Effect of the Method of Inoculation on the Behavior of the Serologic Test for Syphilis in Experimental Syphilis of the Rabbit, Am. J. Syph., Gonor. & Ven. Dis. **34**:25-33 (Jan.) 1950.

24. Rosahn, P. D., and Rowe, C. L.: Experimental Mouse Syphilis: II. Minimal Infectious Number of Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **34**:40-44 (Jan.) 1950.

After incubation periods in the mice of 10 to 13 and 81 to 92 days, lymph nodes from the inoculated mice were subinoculated intratesticularly into rabbits. The minimal number of organisms in the original inoculum capable of producing lesions in rabbits at 10 to 13 days following mouse inoculation was 1,000,000. The comparable value at 81 to 92 days after mouse inoculations was 100,000 organisms, a tenfold difference. It was suggested that, provided certain assumptions are operative, this difference indicates a division time of T. pallidum in the mouse of approximately 24 days. This prolonged division time, in contrast to the division time in the rabbit of 30 to 33 hours, as estimated by other workers, may possibly account, at least in part, for the differing reactions of mouse and rabbit to syphilitic infection.

Susceptibility of Various Strains of Mice and Hamsters to Experimental Syphilis.—Magnuson, Rosenau and Clark [25] studied the suceptibility of nine strains of the laboratory mouse (Mus musculus) to infection with the Nichols strain of T. pallidum, as measured by the infectiousness of their tissue for the rabbit on intracutaneous inoculation. There was wide individual variation in the infectiousness of tissues, not only among strains of mice but within the same strain. None of the strains developed symptomatic infections. No correlation was found between resistance to infection and pigmentation of the host. In order of decreasing susceptibility the strains were CFW, CF-1, C_3H, CW, C-57 black, Chocolate, dba-line 1, State Laboratory and Brown Spot. In order of decreasing infectiousness, the tissues were spleen, liver, brain, blood, lymph node and skeletal muscle. The reasons for these strain variations are obscure, but experiments employing the mouse as a host should allow for this factor.

Johnson [26] reported a series of five experimental procedures, using the golden hamster as the test animal. He could not demonstrate transmission of syphilis by coitus, nor could he prove transmission of infection from syphilitic parents to the newborn. The absence of infection was demonstrated by negative results on dark field examinations, by lack of immunity and by failure of organ emulsions to cause syphilomas when inoculated into rabbits.

Experimental Chemotherapy in Mouse and Rabbit Syphilis.—By a special technic in syphilitic mice Rosahn and Rowe [27] showed that crystalline penicillin G was three times as effective in suppressing infection as sodium penicillin and about 20 times as effective as crystalline penicillin X. In syphilitic infection of three animal species it was demonstrated that the mouse requires considerably larger doses of penicillin than does the rabbit, which in turn requires more of the preparation than man. Evidence cited by the authors suggests that infectious relapse occurs in the syphilitic mouse.

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25. Magnuson, H. J.; Rosenau, B. J., and Clark, J. W., Jr.: The Susceptibility of Various Strains of Mice to Experimental Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:308-317 (July) 1949.

26. Johnson, S. A. M.: Experimental Syphilis in the Golden Hamster: Failure to Transmit Infection by Coitus and from Syphilitic Parents to the Newborn, Arch. Dermat. & Syph. **60**:190-195 (Aug.) 1949.

27. Rosahn, P. D., and Rowe, C. L.: Experimental Mouse Syphilis: III. Bio-Assay of Sodium Penicillin and of Penicillins X and G by a Mouse-Rabbit Technique, Am. J. Syph., Gonor. & Ven. Dis. **34**:167-176 (March) 1950.

Experimental data reported by Eagle [28] demonstrate clearly that the amount of penicillin necessary to abort a syphilitic infection in rabbits increases greatly with the number of organisms inoculated. Rabbits inoculated with 20, 2,000 or 20,000 T. pallidum and treated four days later with a single injection of amorphous penicillin in oil and beeswax required 200, 500 and 3,500 units per kilogram of body weight, respectively, for a 50 per cent cure rate. The necessity for larger doses of penicillin is attributed to the longer time for which effectively bactericidal concentrations of penicillin must be provided in order to kill the larger number of organisms.

Kolmer [29] employed four repository penicillin compounds in the treatment of acute syphilitic orchitis and generalized syphilis of rabbits. Sodium penicillin G in refined peanut oil and beeswax, procaine penicillin G in aqueous suspension, procaine penicillin G in sesame oil and procaine penicillin G in refined peanut oil with 2 per cent aluminum monostearate were employed in eight and 15 day treatment schedules. In general terms the curative activity of crystalline procaine penicillin G was approximately the same as that of crystalline sodium penicillin G in the treatment of experimental syphilis of rabbits. However, all three procaine penicillin G products employed were somewhat less curative than the sodium penicillin G suspended in peanut oil and beeswax. The total curative dose of sodium penicillin G in peanut oil and beeswax administered once a day for eight days was approximately 8,000 units per kilogram of body weight. When administered once a day for 15 days, the total curative dose was reduced to approximately 3,000 units per kilogram. The total curative doses of all four of the penicillin repository products were higher in the treatment of generalized syphilis than in the treatment of acute syphilitic orchitis of rabbits. Thus, in the eight day treatment schedule they were approximately three to five times higher and two to three times higher in the 15 day schedule. Oxophenarsine hydrochloride (mapharsen®) given by intravenous injection and bismuth salicylate in oil administered intramuscularly were found to be synergistic with crystalline procaine penicillin G. Oxophenarsine hydrochloride was found to be somewhat more synergistic than bismuth salicylate with the four repository penicillin products employed. Because of this synergistic activity, Kolmer believes that the therapeutic value of such combined chemotherapy of human syphilis will be ultimately established. Iodides were also shown to act synergistically with penicillin in the treatment of experimental syphilis of rabbits.

Continuing their systematic study of therapy, Kolmer and Rule [30] reiterate that penicillin and iodides act synergistically or additively in the treatment of experimental syphilis of rabbits. However, the combined treatment of acute syphilitic orchitis of rabbits with penicillin and monosodium N-phenylglycinamide-*p*-arsonate (tryparsamide®) may show some degree of synergistic or additive spirocheticidal

28. Eagle, H.: The Effect of the Size of the Inoculum and the Age of the Infection on the Curative Dose of Penicillin in Experimental Infections with Streptococci, Pneumococci, and Treponema Pallidum, J. Exper. Med. **90**:595-607 (Dec.) 1949.

29. Kolmer, J. A.: The Treatment of Acute Syphilitic Orchitis and Generalized Syphilis of Rabbits with Repository Penicillin Products Alone and in Combination with Mapharsen and Bismuth Salicylate, Am. J. Syph., Gonor. & Ven. Dis. **34**:45-56 (Jan.) 1950.

30. Kolmer, J. A., and Rule, A. M.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: V. The Synergistic or Additive Activity of Penicillin Injected Intramuscularly with Sodium Iodide Administered Orally and Intravenously, Arch. Dermat. & Syph. **61**:49-55 (Jan.) 1950; VI. The Synergistic or Additive Activity of Penicillin Injected Intramuscularly and Tryparsamide Administered Intravenously, ibid. **61**:56-62 (Jan.) 1950; II. The Synergistic or Additive Activity of Penicillin, Oxophenarsine Hydrochloride and Bismuth and Potassium Tartrate, ibid. **56**:179-186 (Aug.) 1947.

activity, but these effects are not nearly as pronounced as those on combined treatment with penicillin and oxophenarsine hydrochloride or on combined treatment with penicillin and bismuth.

In another study, Kolmer and Rule [31] report that tryparsamide® in multiple doses shows some degree of additive or synergistic activity when administered along with multiple doses of bismuth subsalicylate in the treatment of acute syphilitic orchitis of rabbits.

LUETIN

Luotest,® a cutaneous test with syphilitic tissue extract (described in last year's review [1]), was performed by Grillmayr [32] in 120 cases. A repeated test after six days, with comparison of the results with those of blood tests, was made in 110 cases. According to Rottmann, an activation of the effect is possible. The reaction proved to be negative in all nonsyphilitic cases except one and was found positive in 54 cases of syphilis (different stages). In 33 cases the diagnosis was made by luotest,® and in 8 cases reactions to blood tests became positive. According to Grillmayr, the reaction is highly specific and should be given further trial.

IMMUNITY IN SYPHILIS

Magnuson has continued his already extensive work on the factors conditioning the development and persistence of immunity in syphilis. Linked closely with susceptibility, the idea of the existence of natural immunity for this disease is partially upheld by Marcussen and Rendal's important observations on syphilis in a Greenland community.

Immunity in Experimental Syphilis.—Magnuson, Rosenau and Clark [33] report the results of a continuation of their earlier studies attempting to measure quantitatively the degree of acquired immunity in experimental rabbit syphilis. In this paper they describe the degree of established immunity as measured by challenge at varying time intervals after termination of the original 12 week immunizing infection. The rabbits immunized by a syphilitic infection of 12 weeks' duration and terminated by penicillin therapy failed to show any change in immunity measured 6, 12, 24 and 48 weeks after treatment, when given a quantitative challenge with the homologous (Nichols) strain. No symptomatic reinfections were obtained with inoculums as large as 2×10^8 organisms. The asymptomatic 50 per cent infectious inoculum was approximately 5×10^8 organisms. No increase in serum reagin titer occurred, regardless of whether reinoculation was followed by asymptomatic infection or no infection.

In another study made by Magnuson, Thompson and Rosenau,[34] in which were employed quantitative measurements of the rates of development of acquired immunity in the rabbit during subcurative therapy with penicillin as

31. Kolmer, J. A., and Rule, A. M.: Tryparsamide and Bismuth Subsalicylate in the Treatment of Experimental Syphilis of Rabbits: Synergistic or Additive Activity, Arch. Dermat. & Syph. **61**:271-275 (Feb.) 1950.

32. Grillmayr, W.: Erfahrungen mit der Luotestwiederholungsimpfung, Wien. med. Wchnschr. **99**:486-489 (Oct. 22) 1949.

33. Magnuson, H. J.; Rosenau, B. J., and Clark, J. W., Jr.: The Duration of Acquired Immunity in Experimental Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:297-302 (July) 1949.

34. Magnuson, H. J.; Thompson, F. A., Jr., and Rosenau, B. J.: The Effect of Subcurative Penicillin Therapy upon the Rate of Development of Acquired Immunity in Experimental Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **34**:219-226 (May) 1950.

compared with the untreated infection, they found that during the subcurative infection additional immunity may develop. The rate of development of this immunity is estimated to be only one-sixth that of the untreated infection. The authors' data suggest that if treatment schemes used prior to intensive treatment required a significant time to cure the patient, there must be significant additions to the total acquired immunity developed by the patient before his infection was cured. It is impossible to determine to what extent differences in immunity status or differences in sexual environment, or perhaps other factors, may account for the observed differences in reinfection rates following intensive treatment as compared with the old standard treatment. The present data suggest, however, that older treatment methods may have permitted the development of considerably more immunity than is permitted with intensive treatment. The difficulties in translating these results to man are enormous. Nevertheless, the concept that the rate of development of acquired immunity to the syphilitic infection may be materially modified by subcurative therapy is probably applicable to the infection in man.

Natural Immunity in Man.—Marcussen and Rendal [35] describe syphilis in a Greenland community. In 1947 a man with primary and secondary syphilis visited a syphilis-free south Greenland community. In a five month period he had sexual intercourse with seven natives, four of whom contracted syphilis. These four in turn had sexual intercourse with fourteen male natives, only one of whom contracted syphilis. He in turn had intercourse with three native women, none of whom contracted syphilis. Measures taken by the city fathers to prevent the spread of the disease included quarantine, an examination (clinical and serologic) each week for nine weeks of every member of the community involved (population, 141) and a careful search for contacts to prevent further spread of the disease. Greenland is the only country in which syphilis does not yet have a secure footing.

Antibodies in Syphilis.—Intravenous injections of suspensions of spirochetes (Reiter's strain) into nonsyphilitic persons result in the appearance of antibodies similar to those in syphilitic serums, according to Puccinelli and Bellone.[36] These authors reported, however, that when these organisms were injected intramuscularly no antibodies appeared in the circulating blood.

Antagonism Between the Virus of Lymphogranuloma Venereum and T. Pallidum.—Levaditi and Vaisman [37] present unconvincing evidence for an "antagonism" between the virus of lymphogranuloma venereum and T. pallidum.

PROGNOSIS

Little of note has appeared on the prognosis of syphilis during this review period. Pesare and his co-workers [38] found during 16 years of observation that a higher mortality rate in each 10 year age group existed among 231 untreated

35. Marcussen, P. V., and Rendal, J.: A Study of Syphilis in a Greenland Community, Ugesk. f. læger **111**:1-5 (Jan.6) 1949; abstracted, Bull. Hyg. **24**:315 (May) 1949; A Study of Syphilis and Sexual Habits in Greenland, Am. J. Syph., Gonor. & Ven. Dis. **34**:144-152 (March) 1950.

36. Puccinelli, V. A., and Bellone, A. G.: La formazione ed il comportamento degli anticorpi treponémici e lipoideo nell'uomo per l'introduzione di spirochete (ceppo coltivabile di Reiter), Gior. ital. dermat. e sif. **40**:362-374 (Sept.-Oct.) 1949.

37. Levaditi, C., and Vaisman, A.: Antagonisme entre le virus lymphogranulomateux et le treponema pallidum, Ann. Inst. Pasteur **78**:404-406 (March) 1950.

38. Pesare, P. J.; Bauer, T. J., and Gleeson, G. A.: Untreated Syphilis in the Male Negro, Am. J. Syph., Gonor. & Ven. Dis. **34**:201-213 (May) 1950.

syphilitics than among 192 nonsyphilitic controls. In those 25 to 54 years of age at the time of the first examination more disabling conditions involving the heart, aorta and other parts of the body were observed among the untreated syphilitic patients. Among persons 55 years of age and over at the time of first examination there was no difference in the incidence of disabling processes. A significant difference in combined mortality and morbidity in the two groups was demonstrated when certain factors were adjusted.

According to Bauer,[39] the death rate due to syphilis has decreased appreciably in the past 10 years. In 1938 the rate was 16 per 100,000 population and in 1948 the rate was 8. The nationwide venereal disease program was initiated in 1936. Since then the rates have been decreasing. The death rate from dementia paralytica in the nonwhite population seemed resistant to control measures, particularly from 1942 to 1946. Later years have shown improvement, and a considerable decline has been noted in all forms of late syphilis. The infant mortality rate from syphilis has decreased since the control program was initiated. Since 1938 this decline has been more notable.

DIAGNOSIS OF SYPHILIS

Progress has continued in the laboratory diagnosis of syphilis. In the field of microscopy, since the electron and phase contrast microscopes are not as yet adaptable to clinical work, reliance for rapid identification of T. pallidum must be placed on the dark field microscope. In a study which is a "must" for all students of syphilology, Reynolds and Hesbacher[40] discuss in detail the principles of dark field microscopy and its application to clinical syphilology.

Serodiagnosis.—There are still many unknowns in the serology of syphilis, and steps are being taken to probe them. Serologic conferences are planned; more work is being done in establishing new tests, proper antigens and other reagents employed in the serologic tests for syphilis. In the sphere of biologic false reactions, the immobilization test of Nelson and Mayer,[41] described in the previous review,[1] is receiving further study.

International Serological Laboratory Congress.—The Subcommittee on Serology and Laboratory Aspects of the Expert Committee on Venereal Disease at its first session, held in Washington, D. C., October 1949,[42] devoted a major part of the discussions to the question of the International Serological Laboratory Conference, which the World Health Organization proposes to convene in 1951 or 1952. The need to hold a laboratory conference is urgently felt, since present technics for serodiagnosis of syphilis lack uniformity; different methods of reporting results of serologic tests lead to confusion. The new serologic tests used in the United States, as the cardiolipin tests or Nelson's treponemal antibody technic, have not been tried in other countries. Organization of the conference on a worldwide scale is important not only on the above technical grounds but also for the procurement of serums from various parts of the world to evaluate the tests properly and to choose reactions adapted to the various areas. The establishment of uniformity in sero-

39. Bauer, T. J.: Mortality from Syphilis, J. Ven. Dis. Inform. **31**:95 (April) 1950.

40. Reynolds, F. W., and Hesbacher, E. W.: Darkfield Microscopy: Some Principles and Applications, J. Ven. Dis. Inform. **31**:17-23 (Jan.) 1950.

41. Nelson, R. A., and Mayer, M. M.: Immobilization of Treponema Pallidum in Vitro by Antibody Produced in Syphilitic Infection, J. Exper. Med. **89**:369-393 (April) 1949.

42. Serology of Syphilis, Chron. World Health Organ. **4**:41-45 (Feb.) 1950.

diagnostic methods is strongly desired. Further progress in the objectives and plans for this conference was reported by the Committee in May 1950.

New Tests.—1. New Flocculation Technic for Syphilis (Chediak Test): Revival of interest in the Chediak test is the subject of several reports. Hogan and Busch [43] describe a flocculation test for syphilis, using the concepts of the Zimmerman and Chediak tests. This test employs whole dried blood absorbed on filter paper. Sufficient blood is obtainable from a finger prick. The test is of especial value in field work, eliminating the difficulties that may arise in the collection of blood specimens from infants in the diagnosis and treatment of congenital syphilis. The test is not intended as a rapid short-cut method, for it requires time and skill as does any other serologic test. The blood is obtained following a finger prick; strips of filter paper are saturated with blood, then allowed to dry. Four ⅜ inch (1 cm.) squares are placed in the concavity of a pyrex® plate, and 0.1 cc. of 0.9 per cent saline solution is added. After rotation procedures, the fluid is expressed from the filter paper by means of forceps. One drop of Venereal Disease Research Laboratory (VDRL) antigen is then added, and the material is again agitated. Reactions are read microscopically. Large and small aggregations are interpreted as a positive reaction. No clumping to slight roughness is considered as a negative result. Quantitative serologic reactions can be determined by varying the number and size of saturated filter paper strips in the test.

2. Härö Method: Härö [44] has used the following method: A piece of blotting paper with the absorbed blood is placed on a glass provided with a depression. On this sample are dropped antigen prepared from the Meinicke reagent and normal human blood serum, and the sample is left in a humid closed vessel at room temperature. The reaction is read microscopically as in the Chediak test. The method is meant for use in mass examinations. Three hundred and four serums from syphilitics were examined simultaneously by Wassermann and Kahn tests and by the author's blotting paper method. The blotting paper test was nearly as sensitive as the Wassermann test but less sensitive than the Kahn test. Further investigations continue.

In mass examinations for syphilis, Härö [45] has compared results of the Chediak test with the results of the Wassermann (WaR), sensitized Wassermann (Chol. WaR) and Kahn tests in serums from 442 syphilitic and 318 nonsyphilitic subjects. He concludes that this test is useful neither in diagnosis nor in mass examination for syphilis. This is regrettable because of the great need for a reliable simple procedure, such as the Chediak test.

3. Ford Robertson and Colquhoun Modification of the Meinicke Clarification Reaction: McMenemey and Whitehead [46] found the Ford Robertson and Colquhoun clarification test (F.R.C.) reliable for the serodiagnosis of syphilis. The

43. Hogan, R. B., and Busch, S.: Filter Paper Microscopic Test for Syphilis, or the FPM Test: A Preliminary Report, J. Ven. Dis. Inform. **31**:37-45 (Feb.) 1950.

44. Härö, S.: The Use of Blood Absorbed by Blotting-Paper in Screen Tests for Syphilis, Sotilaslääket, Aikakausl, 19-28; abstracted, Excerpta med. XIII **4**:117 (March) 1950.

45. Härö, S.: On the Chediak Test, Duodecim **65**:711-716, 1949; abstracted, Excerpta med. XIII **4**:116 (March) 1950.

46. McMenemey, W. H., and Whitehead, W. H.: The Ford Robertson and Colquhoun Modification of the Meinicke Clarification Reaction Compared with the Harrison-Wyler Wassermann and the Standard Kahn Reactions, Together with a New Method of Notation, Brit. J. Ven. Dis. **25**:147-154 (Sept.) 1949.

sensitivity, with certain reservations, and specificity are considered to be favorable and to compare well with that of other established methods, while the simplicity of the test is a strong point in its favor. A numerical method of notation is suggested, and evidence is adduced to show that it provides an effective semiquantitative index of either the amount of reagin present or the severity of the infection. The phenomenon of inhibition and the problem of the false negative reaction are also discussed.

NATURE OF ANTIGENS

Rein and Kostant [47] present in concise form an important review, which should be read in the original, of the present concepts of the nature of antigens and antibodies in the syphilitic serum. Papers on the multiplicity of antibodies produced by T. pallidum are included.

Kahn Antigen: Standards.—Several years ago the Michigan Department of Health Laboratories, in collaboration with Serology Laboratory of the University of Michigan, adapted certain criteria for a Kahn antigen and the establishment of a reference antigen to be used as a guide in standardizing all antigens for use or distribution by either laboratory or for checking antigens received by other laboratories for study. The purpose was primarily to obtain a high degree of uniformity in serologic tests throughout the state. Criteria for the acceptable Kahn antigen are discussed. The procedure of testing a new antigen is now detailed by Kendrick and Kahn.[48]

Titration of Wassermann Antigen.—Price [49] states that the qualities of an antigen in a complement fixation test are the following: It has complement-fixing ability in a serum containing a suitable antibody; it must not have undue anticomplementary property, and the "gap" between its anticomplementary titer and its complement-fixing titer must be wide enough to permit its use with safety in the test, and, finally, the product must be titrated by the method of optimal proportions. The author suggests that in the standardization of any proposed antigen, the following three steps be taken: 1. The antigen must be shown to have complement-fixing ability. 2. The anticomplementary action of the antigen must be determined by itself and in the presence of normal serum. 3. The antigen must be titrated by the method of optimal proportions. The author describes a technic of standardizing the Wassermann antigen. This is based partly on the work of Griffith and Scott (1920).

Vegetable Extract Used as Antigen for Kahn Test.—In 1949 Stevenson [50] showed that a substance with properties akin to those of syphilis "antigen" can be extracted from commercial soybean flour. The most satisfactory method is detailed. The author concluded that when fresh the extract of soybean flour reacted comparatively strongly with about 80 per cent of the positive serums tested, but when

47. Rein, C. R., and Kostant, G. H.: Nature of Antigens and Antibodies in Serology of Syphilis, Arch. Dermat. & Syph. **60**:217-226 (Aug.) 1949.

48. Kendrick, P. L., and Kahn, R. L.: Uniformity of Kahn Antigen: Mutually Established Criteria for an Acceptable Antigen and the Use of a Reference Antigen by the Michigan Department of Health Laboratories and the Serology Laboratory of the University of Michigan Hospital, J. Ven. Dis. Inform. **31**:104-107 (April) 1950.

49. Price, I. N. O.: Complement-Fixation Technique: II. The Titration of the Wassermann Antigen, Brit. J. Ven. Dis. **26**:33-36 (March) 1950.

50. Stevenson, J. S.: A Vegetable Extract Used as an Antigen for the Kahn Test: An Experimental Trial, Brit. J. Ven. Dis. **26**:29-30 (March) 1950.

four weeks old it produced unreliable results because of the development of hypersensitivity. It is suggested that these observations indicate the reason vegetable antigens in general are unsuitable for use in serologic tests for syphilis.

Macnab,[51] of Johannesburg, South Africa, also reports in a preliminary note on the occurrence of a fraction derived from the soybean which, when mixed with an extract of egg yolk, is serologically active in cases of syphilis.

Preparation of Phospholipin and Purified Lecithin.—Letonoff [52] presents a detailed note on an alternate method for the preparation of serologically active phospholipin and purified lecithin for laboratory workers to whom a colloidal mill and stirring mechanism are not available. The latter are required in Letonoff's original method (1948).

Rosenberg [53] gives a preliminary report on the satisfactory results obtained with dipalmityl lecithin in the cardiolipin test.

Cardiolipin Antigen.—Cardiolipin antigen continues to be a bone of contention between two groups, those in favor of its use [54] and those opposed.[55] Dorsey [54e] believes that cardiolipin, combined with lecithin and cholesterol in optimum proportions, constitutes an antigen for the serodiagnosis of syphilis which has been shown by numerous investigations to be superior in specificity and sensitivity to the standard lipid antigens in use. Results are more uniform, and in some cases test reactions are more easily read than those obtained with standard antigens. In addition, antigen emulsions used in flocculation tests are more stable than regular antigens. Cardiolipin is not the perfect antigen. False reactions still occur. However, the demonstrated superiority makes this antigen more desirable in the event two or three methods for its employment are selected and standardized.

Role of Cardiolipin Antigens in the Serology of Syphilis.—Arnold and Mahoney [54a] are of the opinion that the role of cardiolipin antigen in the serology of syphilis and nonspecific diseases should be delineated. The increase of specificity

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51. Macnab, G. M.: Preliminary Note on Occurrence of a Fraction in Soya Bean Serologically Active in Cases of Syphilis, Am. J. Clin. Path. **20**:61-63 (Jan.) 1950.

52 Letonoff, T. V.: Note on an Alternate Method for the Preparation of Serologically Active Phospholipin and Purified Lecithin, Am. J. Clin. Path. **20**:64 (Jan.) 1950.

53. Rosenberg, A. A.: Serologic Activity of Dipalmityl Lecithin: Preliminary Report, J. Ven. Dis. Inform. **30**:194-195 (July) 1949.

54. (*a*) Arnold, R. C., and Mahoney, J. F.: The Role of Cardiolipin Antigens in the Serology of Syphilis, J. Ven. Dis. Inform. **30**:217-219 (Aug.) 1949. (*b*) Silliphant, W.; Engelfried, J. J.; Ellis, G. S., and Butterfield, B.: Cardiolipin-Slide and Standard Kahn Tests for Syphilis: A Comparative Study, U. S. Nav. M. Bull. **49**:995-1004 (Nov.-Dec.) 1949. (*c*) Hasselmann, C. M.: Über serologische Luesreaktionen und eigene Erfahrungen mit dem neuen "Cardiolipin" Antigen, Ztschr. f. Haut.- u. Geschlechtskr. **8**:167-177 (March) 1950. (*d*) Hinton, W. A.; Stuart, G. O., and Grant, J. F.: The Use of Cardiolipin Lecithin in the Preparation of Antigen for the Hinton Test, Am. J. Syph., Gonor. & Ven. Dis. **33**:587-592 (Nov.) 1949. (*e*) Dorsey, D. B.: Experience with Cardiolipin, Illinois M. J. **95**:350-355 (June) 1949. (*f*) Klein, S. J.; Konwaler, B. E.; Sears, C.; Berke, M., and Leiby, G. M.: Cardiolipin Antigen in the Kline Test for Syphilis: III. Further Studies on Optimal Cardiolipin-Lecithin Ratio, Am. J. Syph., Gonor. & Ven. Dis. **34**:245-261 (May) 1950. (*g*) Price, I. N. O., and Wilkinson, A. E.: Comparative Serum Testing with Cardiolipin and Standard Wassermann Antigens: Review of 5,124 Tests, Lancet **1**:14-16 (Jan. 7) 1950.

55. McDermott, E. B., and Kahn, R. L.: Differences in Specificity of Cardiolipin and Kahn Antigens in 1949 National Serologic Evaluation Survey, Univ. Hosp. Bull., Ann Arbor **15**:93-94 (Nov.) 1949. Kvittingen, J.; Cutler, J. C., and Tampi, R. B.: Cardiolipin Antigens in the Serodiagnosis of Syphilis, Indian J. Ven. Dis. **16**:1-4 (Jan.-March) 1950.

by the cardiolipin-lecithin antigen in tests for syphilis seems to indicate that this type of antigen is recommended until more specific reagents are evolved.

Continuing their studies on optimal cardiolipin-lecithin ratio, Klein and his co-workers [54f] reported that the Kahn tests showed 0.11 per cent false positive and 0.63 per cent false doubtful reactions, a specificity of 99.26 per cent. Included with the serums having a negative Kahn reaction were 68 (0.76 per cent) which gave average readings of 001 or 0±1. If these "negative trace" reactions were also subtracted from Kahn specificity, the apparently significant advantage of the Kahn test was lost. Actually, 98.4 per cent of serums in the combined series of presumably nonsyphilitic serums gave negative results with both antigens.

Cardiolipin antigen was compared by Price [54g] with standard Wassermann antigen by the parallel testing of 5,124 serums, using a modified Harrison-Wyler technic. Cardiolipin antigen was appreciably more sensitive than the standard antigen, detecting a higher proportion of cases of early primary syphilis and continuing to give a positive reaction in cases of treated syphilis after other test reactions had been reversed to negative.

Spirochetal Antigen.—This antigen, introduced into this country by Eagle and his co-workers [56] a number of years ago, is the subject of two recent studies.[57]

Pezzi [57a] has used antigens derived from cultivated spirochetes in complement fixation tests for syphilis with results he considers to be favorable. He describes three antibodies in the serums of syphilitic patients that can be differentiated serologically by the use of these antigens: one of a lipid nature, chemically identifiable with the lipids obtained from normal tissues, and two of unknown chemical composition which are probably of a proteinic nature. The author admits that there are discrepancies between the results obtained with beef heart antigens and those obtained with spirochetal antigens, but he considers these discrepancies to be of fundamental significance which ultimately may prove to be of practical value to clinicians in the management of their patients.

Biologic False Positive Reactions.—Ether Anesthetization and Alcohol: Gross [58] reports that after prolonged ether anesthetization the serums of nonsyphilitic persons may give temporarily false positive reactions to serologic tests for syphilis. He also studied the effect of alcohol, both in vitro and in vivo, but in no case did he observe a biologic false positive reaction. Indeed, the author suggests that the serologic reactions of patients with only small quantities of circulating reagin may temporarily become negative following the consumption of alcohol.

Leprosy: Singh [59] reports that 64 specimens of blood from clinically nonsyphilitic lepers from the leprosy hospital at Hendala, Ceylon, were subjected to

56. Eagle, H., and Erickson, P. T.: Evaluation of Spirochete Complement Fixation Reaction in Comparison with the Eagle Flocculation and Wassermann Procedures, J. Ven. Dis. Inform. **21**:31 (Feb.) 1940. Eagle, H., and Hogan, R. B.: On the Presence in Syphilitic Serum of Antibodies to Spirochetes, Their Relation to So-Called Wassermann Reagin, and Their Significance for the Serodiagnosis of Syphilis, J. Exper. Med. **71**:215-230 (Feb.) 1940.

57. (*a*) Pezzi, R.: Sul valore della reazione di Wassermann eseguita con gli antigeni treponemici, Terapia **35**:23-27 (Jan.-Feb.) 1950. (*b*) Puccinelli, V., and Pezzi, R.: Il significato ed il comportamento degli anticorpi antitreponemici ed antilipoideo del siero dei luetici nella practica clinica, Gior. ital. dermat. e sif. **40**:229-262 (July-Aug.) 1949.

58. Gross, H.: Der Einfluss der Narkose und des Alkoholgenusses auf den Ausfall der Luesreaktion, Ztschr. f. Haut- u. Geschlechstkr. **7**:223-225 (Sept. 15) 1949.

59. Singh, B.: False Positive Serological Reactions for Syphilis in Leprosy, Brit. J. Ven. Dis. **25**:159-160 (Sept.) 1949.

serologic study. The results of these tests indicated a high incidence of false positive Wassermann and/or Kahn reactions, e. g., in both lepromatous and neural leprosy.

Erythema Multiforme: Saunders [60] reviewed the 234 cases of erythema multiforme exudativum reported in the literature in English since 1920, and he could find none with a false positive reaction. He reported in detail a case of erythema multiforme exudativum in a young Negro who had positive serologic reactions (as high as 80 Kahn units, 4 + Mazzini and 4 + Wassermann reactions) for about six weeks while he was observed during the third recurrence of his dermatosis. During the first and second attacks there was no serologic abnormality. His serologic reactions became negative without treatment.

Treponemal Immobilization Tests on Normal and Syphilitic Serums.—Magnuson and Thompson [61] undertook a study to evaluate the observations on the treponemal immobilization test recently reported by Nelson and Mayer.[1] It was the purpose of the authors to determine the precision of Nelson's technic on large numbers of serums from normal and syphilitic patients and animals and to establish ways in which the method might be modified to permit more convenient assays. The in vitro test for immobilizing antibodies against T. pallidum as reported by Nelson was performed on serums of 362 patients with syphilis, 81 patients with disease other than syphilis, 73 normal patients and 91 normal rabbits. No positive reactions were encountered in any of the nonsyphilitic persons. In syphilitic patients the immobilizing antibody developed fairly early in the course of the disease. The incidence of positive reactions increased with the duration of the infection. Modifications in technic were suggested that would permit more extended assays with the same amount of materials, such as the employment of smaller volumes to permit assays on larger numbers of serums. Magnuson and co-workers conclude that the immobilizing test is an excellent tool for investigations on immunity and the biologic false positive reaction but feel that the test requires further investigation.

Nelson and co-workers [62] examined the serums from 80 medical students at the Johns Hopkins University whose histories were considered reliable with regard to the absence of syphilitic infection. The serums from the 80 students were negative for immobilizing activity. Serums from 87 patients with diseases other than syphilis were also found to be negative with the immobilization test. All patients in this group were selected as free from syphilis on the basis of a negative history of infection and a negative serologic reaction. The serums from 50 patients with latent syphilis, from 18 patients with asymptomatic neurosyphilis, from 51 patients with late symptomatic syphilis and from 6 patients with untreated late congenital syphilis gave strongly positive immobilization reactions. Serums from 7 persons with late syphilis produced strongly positive treponemal immobilization activity, despite the lack of reactivity with lipid antigens of the three standard serologic tests used. Quantitative titration of immobilizing antibody was done on 15 serums in each of the following categories: normal, primary, secondary, latent and late

60. Saunders, R. H., Jr.: Erythema Multiforme Exudativum: Report of a Case with False-Positive Serology, Yale J. Biol. & Med. **21**:481-486 (July) 1949.

61. Magnuson, H. J., and Thompson, F. A.: Treponemal Immobilization Test of Normal and Syphilitic Serums, J. Ven. Dis. Inform. **30**:309-320 (Nov.) 1949.

62. Nelson, R. A., Jr.; Zheutlin, H. E. C.; Diesendruck, J. A., and Austin, P. G. M., Jr.: Studies on Treponemal Immobilizing Antibodies in Syphilis: II. Incidence in Serum and Cerebrospinal Fluid in Human Beings and Absence in "Biologic False Positive" Reactors, Am. J. Syph., Gonor. & Ven. Dis. **34**:101-121 (March) 1950.

symptomatic syphilis. The titers of these serums were expressed as the serum dilution which produced immobilization of 50 per cent of the treponemes after 18 hours' incubation at 35 C., i. e., the I. $T._{50}$ (18 hours). The 15 normal serums all gave negative reactions. The median titer for the serums of primary syphilis was 60, for the serums of secondary syphilis 810, for the serums of latent syphilis 4,860 and for the serums of late symptomatic syphilis 4,860. Comparative titrations of reagin in these serums were performed with the Eagle and VDRL cardiolipin test procedures. There was a general progressive rise in both reagin and immobilizing titers from primary to secondary syphilis. No correlation existed between the two antibody titers in latent and late symptomatic syphilis.

The immobilizing test was performed on samples of cerebrospinal fluid collected from 25 patients with miscellaneous diseases in whom syphilis was excluded. None of the 25 fluids from patients with disease other than syphilis showed immobilizing antibody. Fluids from 19 patients with latent syphilis were also negative; 2 gave doubtful reactions, and 4 gave positive reactions. All 33 fluids from patients with central nervous system syphilis gave positive immobilizing reactions. Serums from 12 patients with presumed biologic false positive reactions were examined and found to be free of immobilizing antibodies. Additional information regarding the specificity of the immobilization phenomenon indicated that immobilizing antibody was produced regularly as a result of infection with virulent spirochetes of the Treponema group, i. e., T. pallidum, Treponema pertenue and Treponema cuniculi. It was not produced in animals experimentally infected with Leptospira or Borrelia or in animals artificially "immunized" with nonvirulent cultured spirochetes, e. g., of the Reiter, Kazan and S-56 strains.

CEREBROSPINAL FLUID

Kolmer and VDRL Tests.—Victor and Hunter,[63] of the Public Health Laboratories of Topeka, Kansas, found the VDRL test simpler and more easily read than the Kolmer test on the cerebrospinal fluid. In a series of 503 spinal fluids there was complete disagreement of reactions to the two tests in 14 specimens and partial disagreement in 11 specimens. The greatest disagreement occurred in specimens with weak reactions. The disagreement was largely due to the manner of reporting "doubtful" Kolmer and the negative VDRL reactions.

Harding and Harris [64] report observations obtained during an investigation of the effects of temperature on quantitative turbidimetric analysis of protein in the cerebrospinal fluid, using trichloracetic acid in accordance with the procedure followed in the Venereal Disease Research Laboratory. Temperature influences the turbidity when trichloracetic acid is used in determinations of spinal fluid protein. However, accurate quantitative results may be obtained at uncontrolled room temperatures if standard protein solutions are tested simultaneously each day. The protein values for spinal fluids must be calculated by comparison with results obtained on solutions of known protein content that are retested on each test day. This method requires plotting calibration curves each day. It is more practical,

63. Victor, F. M., and Hunter, C. A.: Observation of the Kolmer Complement-Fixation Test and the VDRL Spinal Fluid Test, J. Ven. Dis. Inform. **30**:347-349 (Dec.) 1949.

64. Harding, V. L., and Harris, A.: The Effect of Temperature Variants on Quantitative Turbidimetric Determination of Spinal Fluid Protein, Using Trichloracetic Acid, J. Ven. Dis. Inform. **30**:325-327 (Dec.) 1949.

however, to conduct tests at 37 C. and to prepare a conversion chart from points obtained by tests performed at this temperature.

Total Protein Determination.—Waldman and his associates [65] describe in detail a modification of the VDRL method for determination of total protein content, utilizing only 0.5 ml. of cerebrospinal fluid instead of the usual 2.5 ml. required for testing.

Protein in the Cerebrospinal Fluids of Patients with Multiple Sclerosis.—Kabat and his associates [66] report that increases in the proportion of globulin in the cerebrospinal fluid have long been used as an aid in the diagnosis of various neurological disorders, notably neurosyphilis and multiple sclerosis. This determination has generally been accomplished by a variety of empirical and essentially qualitative procedures, such as the colloidal gold, gum mastic and Pandy tests. Positive colloidal reactions in the cerebrospinal fluid of patients with multiple sclerosis have been reported by various investigators as occurring in 29 to 81 per cent of fluids examined. In recent years electrophoretic studies have established that the gamma globulin, and in some dilutions the beta globulin fractions of cerebrospinal fluid and of serum are responsibile for the colloidal reaction and that these can be inhibited by the electrophoretically separated albumin fraction. Electrophoretic studies have also shown that gamma globulin is elevated in the cerebrospinal fluid of patients with neurosyphilis and multiple sclerosis and that this increase may occur without significant changes in the total protein or albumin. To provide a precise quantitative technic for direct measurement of the albumin and gamma globulin which did not require excessively large quantities of cerebrospinal fluid, an immunochemical method was developed in Kabat's laboratory. Results by this procedure substantiated and extended the earlier electrophoretic observations. The cerebrospinal fluid albumin and gamma globulin were studied in 100 cases of multiple sclerosis. Of these 85 per cent were observed to show an increase in cerebrospinal fluid gamma globulin outside the normal range by one or more of the three criteria established. Values for cerebrospinal fluid albumin were generally normal. The increase in gamma globulin is not specific for multiple sclerosis, since similar findings are obtained in neurosyphilis and in certain other diseases. Increases in cerebrospinal fluid gamma globulin may be also merely a reflection of an abnormally high serum gamma globulin. Comparision of serum and cerebrospinal fluid gamma globulins in the same persons confirms previous conclusions that the cerebrospinal fluid globulin is derived in part from the blood and in part from the tissues of the central nervous system. The estimation of the cerebrospinal fluid globulin is a useful aid in the diagnosis of multiple sclerosis, provided adequate care is taken to exclude the possibility of false positive reactions.

CLINICAL MANIFESTATIONS OF EARLY SYPHILIS

Serum Globulin.—Verhagen [67] has studied the changes in the serum globulin content occurring during early syphilis and has noted its return to normal following

65. Waldman, R. K.; Ullrich, L. F., and Borman, E. K.: Adaptation of the VDRL Method for Total Protein Determination to the Use of Small Quantities of Cerebrospinal Fluid, J. Ven. Dis. Inform. **31**:159-161 (June) 1950.

66. Kabat, E. A.; Freedman, D. A.; Murray, J. P., and Knaub, V.: A Study of the Crystalline Albumin, Gamma Globulin and Total Protein in the Cerebrospinal Fluid of 100 Cases of Multiple Sclerosis and in Other Diseases, Am. J. M. Sc. **219**:55-64 (Jan.) 1950.

67. Verhagen, B. A.: Changes in the Serum Globulin Content in the Development of and the Recovery from Early Syphilis, Acta dermat.-venereol. **29**:443-459, 1949.

suitable antisyphilitic therapy. The Moncke-Sommer test (a modified Takata reaction), the standard formol-gel reaction, the calcium formol-gel reaction and the blood sedimentation rate were used. No significant changes in the serum globulins were noted among patients with seronegative primary syphilis, but (with the calcium formol-gel reaction) there were abnormalities in about half the patients with seropositive primary syphilis and in 97 per cent of patients in the secondary stage of the disease. Usually hyperglobulinemia and an increased sedimentation rate were observed to coexist. The abnormalities disappeared quite rapidly following the institution of antisyphilitic therapy. The author interprets the presence of increased gamma globulins to indicate the mobilization of humoral antibodies against the T. pallidum.

Epitrochlear Adenopathy in Syphilis.—Since it is the usual teaching that bilateral epitrochlear enlargement is uncommon and when found is highly suggestive of syphilis, Chanarin [68] studied 500 natives in the Grahamstown district of South Africa. He reported clinically palpable epitrochlear lymph nodes in 75 per cent of the males and in 54 per cent of the females. A positive Wassermann reaction was obtained in 18.4 per cent of the 500 natives and in 15.9 per cent of those with bilateral epitrochlear nodes. Therefore, the enlargement was unrelated to syphilis. Histological study of excised nodes showed chronic nonspecific lymphadenitis in more than 80 per cent of the nodes. This was probably the result of repeated minor trauma and sepsis. Three nodes removed for histological study (10 per cent) proved to be tuberculous.

Seronegative Secondary Syphilis.—Kuhl and Sauer [69] studied 2,604 cases of secondary syphilis, including 1,732 untreated cases at the West Virginia Medical Center. They discovered 42 cases (1.61 per cent) of seronegative secondary syphilis and 20 cases (1.15 per cent) of untreated secondary syphilis. These selections were based on the reactions to the quantitative Kahn test alone, but, when all available clinical and laboratory data relating to these patients were analyzed, not a single case of proved seronegativity in untreated secondary syphilis was found. They feel that the majority of cases statistically recorded as seronegative in untreated secondary syphilis are erroneous, owing to factors of misdiagnosis, false negative serologic reactions or clerical error.

REINFECTION

Peabody and Webster [70] continue their interest in reinfection in syphilis. They review 140 instances of syphilitic reinfection or relapse occurring in 128 patients at the New York Hospital since 1932. Of the 140 instances of recurrent syphilitic infection, 45 were previously treated with penicillin, 19 with "five day drip" arsenotherapy and 76 with prolonged administration of heavy metals and arsenotherapy. Eight-two of the 140 recurrent infections were considered instances of reinfection; 16, probable or possible reinfection, and 42, relapse. Twelve of the 140 recurrent infections were considered instances of repeated reinfection or relapse. The authors

68. Chanarin, I.: Epitrochlear Adenopathy in the Bantu, South African M. J. **23**:960-962 (Nov. 26) 1949.

69. Kuhl, I. W., and Sauer, G. C.: Seronegative Secondary Syphilis, J. Invest. Dermat. **13**:191-197 (Oct.) 1949.

70. Peabody, G. E., and Webster, B.: Reinfection in Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:334-356 (July) 1949.

show that about 58 per cent of all instances of recurrent infection were considered reinfection, regardless of the type of therapy, i. e., penicillin, "five day drip" arsenotherapy and prolonged heavy metal and arsenotherapy. When all instances of reinfection, including the probable and possible, were included with the undoubted reinfections, the relative percentages were 75.6 per cent for recurrent infections treated previously with penicillin; 73.7 per cent for recurrent infections treated previously with "five day drip" arsenotherapy; 65.7 per cent for recurrent infections treated previously with prolonged administration of heavy metals and arsenic, and 70.0 per cent for the total. Concomitantly, 30.0 per cent of the total number of recurrent infections were relapses. The basis for determining whether or not a given patient had been reinfected with syphilis was the sum total of all facts known of that patient and not exact comparison and agreement with a set of predetermined requirements. The authors stress the need for new criteria in the evaluation of syphilitic reinfection in order to determine more accurately the effectiveness of antisyphilitic therapy.

CLINICAL MANIFESTATIONS OF LATE SYPHILIS

Tuberculoid Gumma.—A case of "tuberculoid gumma," a rare late syphilitic lesion described by Berdal, is reported by Schmidt and his co-workers.[71] This lesion responded clinically and serologically to fever therapy and administration of 4,000,000 units of penicillin, 0.3 Gm. of neoarsphenamine and 0.8 Gm. of a bismuth preparation.

Juxta-Articular Nodes.—Katz[72] reported the case of a 54 year old white Canadian who had multiple juxta-articular nodes with unusual localization on the fingers and palms. The histological changes in this case are characteristic of the condition, consisting of thick collagenous bundles with alternate zones of cellular infiltration.

Syphilitic Bursitis.—Syphilitic bursitis, a comparatively rare form of late syphilis, was reported by Prosser Thomas and Rook[73] in the prepatellar bursa of a 64 year old white woman. The serologic test for syphilis gave a strongly positive reaction, and roentgenologic studies of the bones of the involved knee were normal. The lesion regressed on treatment with bismuth and penicillin.

Syphilis of the Stomach: The Stomach in Syphilis.—Palmer,[74] in his excellent review of the literature on gastric syphilis, describes the gastroscopic appearance of the stomach, as observed by Schwartz in 12 patients with secondary syphilis. According to Schwartz, seven of the 12 patients showed a uniform gastroscopic picture: edematous and hyperemic areas, especially in the mid pars media and proximal to the angulus, with numerous submucosal hemorrhages and occasional scattered erosions, mucus adherent to a friable mucosa and many tiny patches of

71. Schmidt, F. R.; Jaramillo, R., and Donghi, A.: Tuberculoid Gumma (Berdal), a Rare Type of Syphiloderm: Report of a Case, Am. J. Syph., Gonor. & Ven. Dis. **34**:182 (March) 1950.

72. Katz, F.: Syphilitic Juxta-Articular Nodes, Arch. Dermat. & Syph. **60**:426-427 (Sept.) 1949.

73. Prosser Thomas, E. W., and Rook, A. J.: Syphilitic Bursitis with Report of a Case, Lancet **2**:1221-1222 (Dec. 31) 1949.

74. Palmer, E. D.: Syphilis of the Stomach and the Stomach in Syphilis: A Review of the Literature with Particular Reference to Gross Pathology and Gastroscopic Diagnosis, Am. J. Syph., Gonor. & Ven. Dis. **33**:481-496 (Sept.) 1949.

gray-white mucus with surrounding hyperemia, resembling mucous patches of the pharynx. In the other five patients a similar, but less intense, picture was seen. Within three days of completion of penicillin therapy (2,400,000 units) repeat gastroscopy showed an almost normal mucosa in 10 of the 12 patients; there were now only a few submucosal hemorrhages or occasional erosions and minimal edema and redness. No atrophic gastritis was observed during the study. Palmer also covers the literature on other types of syphilitic involvement, i. e., infiltrative lesions, ulcers and tumor types. The gross pathologic appearance, as well as the gastroscopic picture, is described. The effects of syphilis on the gastric secretory function are also reviewed. It appears that there is a definite tendency toward suppression of gastric secretory activity during all stages of syphilis. After specific antisyphilitic therapy, the achlorhydric syphilitic may begin to secrete acid.

In a review of the literature Tartarini [75] points out that gastroduodenal hemorrhages have been observed in patients with tabes dorsalis.

Miliary Syphilomas of the Liver.—In a needle biopsy specimen of the liver Laqueur and Egeli [76] observed granulomatous lesions which by their relation to blood vessels were diagnosed as miliary syphilomas. From a survey of the literature it seems that such lesions of the liver are rare findings. From unpublished observations Laqueur and Egeli, however, are of the opinion that such syphilitic lesions may occur not so infrequently and that the liver perhaps may be regularly involved in the process of early syphilis.

Pleurisy with Effusion in Early Syphilis.—Calnan [77] reports on a man, aged 42, in whom early secondary syphilis, jaundice and pleurisy with effusion were associated. All responded to antisyphilitic therapy. The presence of pleurisy in early syphilis is extremely unusual, no previous similar description being found in the literature. T. pallidum was not demonstrated in the pleural fluid, but evidence was in favor of the illness having only one causative factor.

Syphilis of the Prostate.—Bini [78] has reviewed the medical literature pertaining to syphilitic prostatitis and was able to find 56 reported cases. He expresses the opinion that this condition is commoner than is generally believed, since it is difficult to recognize and may exist as the only overt manifestation of syphilitic infection. There appear to be no pathognomonic symptoms or signs of syphilitic involvement of the prostate gland, and the diagnosis is established by eliminating prostatic gonorrhea, tuberculosis, benign hypertrophy and neoplasm, plus the finding of positive reactions to serologic tests and, most important of all, a prompt response to antisyphilitic treatment. A number of case histories is given, including a report of one case personally observed by the author. The condition has been recorded as early as 14 weeks after infection and as late as 56 years following the chancre. The lesion may be either gummatous or diffuse inflammatory infiltration. Only three cases have been studied histopathologically, and the lesions

75. Tartarini, E.: Gastroduodenal Ulcers as a Result of Lesion or Disease of the Nervous System, Acta med. Scandinav. **134**:346-370, 1949.

76. Laqueur, W., and Egeli, E. S.: Miliare Syphilome der Leber: Befunde mittels der Aspirationsbiopsie erhoben, Schweiz. Ztschr. f. Path. u. Bakt. **12**:306-312, 1949.

77. Calnan, C. D.: Pleurisy with Effusion in Early Syphilis, Tubercle **30**:260-264 (Nov.) 1949.

78. Bini, G.: Contributo allo studio della sifilide della prostata, Arch. ital. dermat., sif. **22**:389-410 (Dec.) 1949.

described are similar to those encountered in other organs. In two cases T. pallidum was observed in the prostatic tissue sections, but the organism has never been isolated from the organ by rabbit inoculation.

Infertility and Sterility Due to Venereal Diseases.—In contrast to gonococcic and nonspecific infections, which cause 20 per cent of the cases of male infertility and an even higher percentage of the cases of female infertility and sterility, syphilis is not an important causative factor. According to Boyd,[79] the seminal fluid is normal on examination in men with congenital syphilis, generalized secondary syphilis, tabes dorsalis and dementia paralytica. In some tabetics, however, impotence is the first noticed symptom and, therefore, may be reason for infertility.

CLINICAL MANIFESTATIONS OF CARDIOVASCULAR SYPHILIS

In the area of cardiovascular syphilis definitive progress in diagnosis has been made during this review period. Especially noteworthy are the studies defining the usefulness of angiocardiography in the diagnosis of syphilitic aortitis.

Diseases of the Aorta.—A complete and entirely modern discussion of all phases of syphilis of the aorta forms one chapter in the recent book by Reich.[80] In addition to tables, photomicrographs and several roentgenograms and angiocardiograms, Reich illustrates his book with several simple, well conceived sketches which facilitate the understanding of various physical diagnostic methods. The treatment of syphilis of the aorta is considered from both the medical and the surgical angles; in the former group he considers therapy with bismuth subsalicylate, potassium iodide and arsenicals, in addition to penicillin; in the latter phase he discusses arteriovenous anastomosis, insertion of foreign bodies, injection of the upper sympathetic ganglions and wrapping the aneurysm in polythene cellophane® (PT 300).

Human Aorta Cholesterol.—Of 50 aortas examined by Faber,[81] in Copenhagen, Denmark, at autopsies for the purpose of determining the deposition of cholesterol, the changes in 12 were diagnosed as syphilitic aortitis. An increase in sulfate corresponding to the increased rate of deposition of cholesterol was noted, probably caused by the inflammatory reaction which seems to determine the sulfate content.

Angiocardiography.—As stated above, angiocardiography has come into its own as a means of facilitating the diagnosis of syphilitic aortitis. Several recent contributors have issued favorable reports.[82]

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79. Boyd, R. H.: Venereal Disease as a Cause of Infertility and Sterility: Assessment and Treatment, Brit. J. Ven. Dis. **25**:179-184 (Dec.) 1949.

80. Reich, N. E.: Diseases of the Aorta, Diagnosis and Treatment, New York, Macmillan Company, 1949, pp. 84-112.

81. Faber, M.: The Human Aorta: Sulfate-Containing Polyuronides and the Deposition of Cholesterol, Arch. Path. **48**:342-350 (Oct.) 1949.

82. (*a*) Gardner, F.: Angiocardiography, Post-Grad. M. J. **25**:553-564 (Nov.) 1949. (*b*) Abbott, O. A.; Hopkins, W. A., and Leigh, T. F.: The Role of Angiocardiography and Venography in Mediastinal and Paramediastinal Lesions, J. Thoracic Surg. **18**:869-898 (Dec.) 1949. (*c*) Steinberg, I., and Dotter, C. T.: The Differentiation of Mediastinal Tumour and Aneurysm: Value of Angiocardiography, Brit. J. Radiol. **22**:567-572 (Oct.) 1949. (*d*) Steinberg, I., and others: Angiocardiography Diagnosis of Syphilitic Aortitis, Am. J. Roentgenol. **62**:655-660 (Nov.) 1949. (*e*) Peabody, G. E.; Reader, G. G.; Dotter, C. T.; Steinberg, I., and Webster, B.: Angiocardiography in the Diagnosis of Cardiovascular Syphilis, Am. J. M. Sc. **219**:242-248 (March) 1950.

Abbott and his co-workers [82b] believe that there is a definite place for use of venography and angiocardiography in the study of mediastinal and paramediastinal masses. Two cases are described in which syphilitic aneurysms were demonstrated by angiocardiogram.

In one report Steinberg and Dotter [82c] advocate angiocardiography as a simple and effective method of differentiating aneurysms from other space-occupying lesions of the thorax. The authors employ a stereocassette changer and have routinely used only two exposures for an injection. Difficulties in diagnosis result from the fact that aneurysms may not show pulsation owing to clotting, while tumors may show transmitted pulsations which are readily resolved by angiocardiography. Four patients are presented, each of whom had a positive serologic reaction. The first patient had a dermoid; the other three had aneurysms. One patient had an aneurysm of the left subclavian artery, in addition to the aneurysm of the aortic arch. The former did not opacify owing to the small size of the orifice communicating with the aorta.

Steinberg and co-workers [82d] performed angiocardiography on 60 patients with syphilitic aortitis. This procedure greatly facilitates the early diagnosis of the complication by revealing clearly the gross anatomy of the entire thoracic portion of the aorta. A diagnosis can often be made with this procedure in the absence of conclusive clinical or roentgenologic evidence. The angiocardiographic signs of syphilitic aortitis include aortic dilatation (the mid portion of the ascending aorta in 51 patients measuring above 38 mm.), irregularity of lumen (51 patients), calcification of ascending aorta (16 patients), aortic tortuosity (51 patients), variations in thickness of the aortic wall and the presence of aneurysm (25 patients). Dilatation, the cardinal angiocardiographic sign of syphilitic aortitis, may also be caused by hypertension, aortic valvular insufficiency of nonsyphilitic origin or coarctation of the aorta. It is not pathognomonic of syphilis of the aorta. Aortic dilatation may be absent in early syphilitic aortitis. Uncomplicated arteriosclerosis apparently does not cause aortic dilatation beyond the upper limit of 38 mm. The diagnosis of syphilitic aortitis may be made sooner and put on a sounder anatomic basis by means of angiocardiography, thus facilitating the earlier more adequate treatment required by the cardiovascular complications of syphilis.

Ninety-three patients at the New York Hospital with and without signs or symptoms of cardiovascular syphilis were studied angiocardiographically (according to the technic of Robb and Steinberg) by Peabody and his associates.[82e] Following the taking of the history, physical examination, laboratory study and routine roentgenograms of the chest, multiple contrast films of the cardiac chambers and associated great vessels were obtained from a distance of 6 feet (1.8 meters) immediately after intravenous injection of contrast substance. Studies were made in the left anterior oblique position. Previous studies revealed that certain structural changes may be found as a consequence of syphilitic aortitis: (1) dilatation of the mid ascending aorta beyond the upper limit of 38 mm.; (2) irregularity of the lumen of the ascending aorta; (3) variations in thickness of the aortic wall; (4) calcification of the ascending aorta, which may be accurately localized with angiocardiography, and (5) tortuosity of the aorta. Of the 93 patients 83 had late acquired syphilis. Of the latter group 49 were found to have cardiovascular syphilis with aortitis, aneurysm or aortic insufficiency; the diseases in 34 of these

could be diagnosed without the aid of angiocardiography, whereas the conditions of the remaining 15 would have been diagnosed as late latent syphilis. Study with intravenously administered contrast medium established the diagnosis of uncomplicated syphilitic aortitis in 13 patients in whom the conventional chest films were normal and in two persons with syphilitic aortitis and aneurysm in whom chest films showed only a mass in the mediastinum. Contrast studies also confirmed the diagnosis of aortic syphilis in 17 patients who had syphilitic heart disease with insufficiency whose chest roentgenogram was normal, as well as in 4 persons having syphilitic heart disease with aortic insufficiency and 1 patient who had syphilitic aortitis with aneurysms in whom the appearance on chest roentgenogram was inconclusive. However, 9 patients with suggestive chest roentgenograms were excluded from the group with cardiovascular syphilis by contrast studies. Aneurysms of the innominate artery were detected in 3 patients and ruled out in another. On correlation of physical findings with angiocardiography, it was found that the presence of an aortic systolic murmur and prolonged second aortic sound is of little value in detection of syphilitic aortitis, since they were heard in three fifths of patients without cardiovascular syphilis and were present in only six of the 16 patients with uncomplicated aortitis. Angiocardiography is a valuable instrument in the early diagnosis of syphilitic aortitis. This method will also denote nonvascular masses and reveal unsuspected aneurysms of the aorta and its branches. It is suggested that this procedure be used to aid in detecting cardiovascular syphilis in patients with late syphilis.

Calcification in Syphilitic Aortitis.—The importance of calcification as a diagnostic sign of syphilitic aortitis is clarified by Thorner, Carter and Griffith.[83] Of their 122 patients with syphilitic aortitis 22 (18 per cent) showed calcification of the ascending aorta, as compared with 2 (2 per cent) of the 100 nonsyphilitic persons with atherosclerosis of the aorta. The serologic test for syphilis gave a positive reaction in 16 (72.7 per cent) of the 22 syphilitic patients with calcification and in 86 (86 per cent) of the patients without calcification. In the group exhibiting calcification, the age level was older and the duration of the syphilitic process was longer. Inasmuch as the walls of the aorta are in constant motion, slow exposures used in routine chest films will blur the calcifications and make their detection difficult or impossible. Rapid exposures (1/20 to 1/30 second), using sufficiently heavy exposure to reveal detail in the cardiomediastinal opacity, will reveal the lime salt deposits early. In this series 20 per cent of the patients in the noncalcific group showed calcification at autopsy which was not detected by the routine film technics used. The presence of calcification of the ascending aorta is of value in the differential diagnosis of aortic insufficiency as to rheumatic, syphilitic or arteriosclerotic cause. It is also of value in distinguishing thoracic aneurysm from neoplasms. The presence of calcification implies the presence of syphilis and may swing the balance in favor of the diagnosis of syphilitic aneurysm.

Elkeles[84] also indicated from study of only one patient that detection of linear calcification of the ascending aorta on roentgenograms suggests syphilitic aortitis.

83. Thorner, M. C.; Carter, R. A., and Griffith, G. C.: Calcification as a Diagnostic Sign of Syphilitic Aortitis, Am. Heart. J. **38**:641-653 (Nov.) 1949.

84. Elkeles, A.: Calcification of Ascending Aorta as a Diagnostic Sign of Syphilitic Aortitis, Proc. Roy. Soc. Med. **42**:867-868 (Nov.) 1949.

Syphilitic Aortitis with Obstruction of the Multiple Aortic Ostiums.—Barker [85] reports a case of syphilitic aortitis and endarteritis in which there were obliteration of the lumen of the innominate artery, partial obstruction to the lumen of the left subclavian artery and almost complete occlusion of the coronary ostiums. The patient died of myocardial infarction without actual coronary thrombosis 10 months after onset of symptoms, despite penicillin therapy. The diagnosis of disease of the coronary ostiums should be considered when in association with electrocardiographic changes of "global ischemia" there is evidence of other ostial obstruction, with or without a demonstrable aortic aneurysm.

Diagnosis During Life of Stenosis of the Coronary Ostiums.—Gottlieb [86] reported three instances of syphilitic stenosis of the coronary orifices which were diagnosed during life. It is surprising that this diagnosis is not made oftener during life, in view of the fact that the incidence of stenosis of coronary orifices in cases of syphilitic aortitis has been reported as high as 35 per cent at autopsy. Although its recognition is largely inferential, the following points may aid in making a clinical diagnosis: (1) the keeping in mind of its frequent association with aortic insufficiency; (2) the fact that cardiac symptoms appear at an earlier age in cases of aortic insufficiency when the coronary arteries are affected; (3) the observation that cardiac pain and dyspnea are its commonest attendants; when these occur in a patient under 40 years of age, especially in a Negro who has both syphilitic aortitis and aortic insufficiency, ostial involvement should be suspected, and (4) the observation that occurrence of paroxysms of nocturnal dyspnea or attacks of pulmonary edema, provided coronary arteriosclerosis is not present, suggests stenosis or occlusion of one or both coronary orifices. The making of a diagnosis of syphilitic stenosis of the coronary ostiums throws considerable light on a case of coronary insufficiency, inasmuch as it signals a short course and probable sudden death.

Syphilitic Aneurysm with Rupture into the Pulmonary Artery.—Klein and Porter [87] describe a 40 year old man whom they observed for 14 months after correctly diagnosing his condition as syphilitic aneurysm of the aorta with rupture into the pulmonary artery. They performed catheterization of the right auricle and ventricle and the pulmonary artery and noted increased pressure in the right ventricle and pulmonary artery and increased oxygen saturation of the blood in the pulmonary artery. The accuracy of the antemortem diagnosis was due in large part to the use of catheterization as a diagnostic procedure.

Spontaneous Rupture of Syphilitic Saccular Aneurysms of the Aorta.—Goldstein [88] reports 29 cases among the records of the Chief Medical Examiner of the City of New York in which the cause of death was spontaneous rupture of a saccular aneurysm of the intrapericardial portion of the ascending aorta into the pericardial cavity, with resultant hemopericardium and cardiac tamponade. The

85. Barker, W. F.: Syphilitic Aortitis with Obstruction of the Multiple Aortic Ostia, New England J. Med. **241**:524-527 (Oct. 6) 1949.

86. Gottlieb, A. M.: Syphilitic Stenosis of the Coronary Ostia Diagnosed During Life, Postgrad. Med. **6**:372-378 (Nov.) 1949.

87. Klein, A., and Porter, W. B.: Syphilitic Aneurysm of the Aorta with Rupture into the Pulmonary Artery, Am. Heart J. **39**:465-472 (March) 1950.

88. Goldstein, P.: Spontaneous Rupture of Syphilitic Saccular Aneurysms of the Ascending Aorta into the Pericardial Cavity, with Hemopericardium, Arch. Int. Med. **84**:540-577 (Oct.) 1949.

aneurysms reported in this series were, as a rule, small and had thinned-out walls. In only two patients was there more than one aneurysm. Only eight of the 29 persons had aneurysms large enough to have been diagnosed ante mortem. The youngest person in the series was a 17 year old Negro girl. The oldest was a white man, aged 78 years. Six persons in the series were 50 years of age or more. Twenty-three of the patients were men, and six were women. Eleven patients were white, and 17 were Negroes. The heart was normal in size in 20 persons and enlarged in nine. Aortic insufficiency due to separation of the commissures was noted in two patients. Ten patients showed some involvement of the mouth of the coronary arteries. The author feels that saccular aneurysms of the ascending aorta may be present in patients that show other evidence of cardiovascular syphilis.

Pulmonary Arteriosclerosis and Arteritis.—Leopold,[89] in his report of a case of arteriolosclerosis, observed at necropsy changes in the aorta compatible with syphilis; there were serious hypertrophy of the right ventricle and intimal proliferation of the small pulmonary arteries, with reduction in their lumens. Similar changes were absent from the small vessels of the greater circulation. Leopold believes that pulmonary arteriolosclerosis occurs most frequently in persons with syphilitic infection, who have in addition a chronic infection of the lower part of the respiratory tract.

Hejtmancik, Bradfield and Rigdon [90] report a case of productive cicatricial pulmonary arteritis in a 56 year old Negro woman with acquired syphilis.

CLINICAL MANIFESTATIONS OF NEUROSYPHILIS

Except for the ocular manifestations of neurosyphilis, little has appeared on the clinical manifestations of neurosyphilis.

Diez-Rivas [91] reports results obtained when the Kepler water test was performed on nine patients with tabes dorsalis. The water test is an aid in the diagnosis of Addison's disease ordinarily. However, unrelated conditions may give a positive result, as nervous exhaustion, hyperthyroidism, hepatic disease, pituitary insufficiency and renal disease. None of these conditions occurred in the patients tested, however. The results show that five tabetic patients had a positive value for factor A; two gave borderline values and one a negative value. One patient had an early neurogenic bladder. The volumetric part of the test was positive for all patients. There was slight increase of blood urea nitrogen in five persons. The variation from normal results was due to an abnormal volumetric part (delayed water diuresis). The average values for the plasma and urinary chloride ion and urinary urea nitrogen were normal. The explanation of the abnormal changes in the test in these patients is not clear. It would be necessary to evaluate the individual person and compute factor A, as recommended by Kepler, before accepting the results of the test as an indication of Addison's disease or adrenal hypofunction.

89. Leopold, S. S.: The Etiology of Pulmonary Arteriolosclerosis (Ayerza's Syndrome), Am. J. M. Sc. **219**:152-160 (Feb.) 1950.

90. Hejtmancik, M. R.; Bradfield, J. Y., and Rigdon, R. H.: Pulmonary Arteritis Due to Acquired Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **34**:236-244 (May) 1950.

91. Diez-Rivas, F.: The Kepler Water Test in Tabes Dorsalis, J. Lab. & Clin. Med. **34**:830-833 (June) 1949.

CLINICAL MANIFESTATIONS OF OCULAR SYPHILIS

The work on ocular syphilis here reported represents a variety of interests. Especially noteworthy is the study by Klauder and Meyer, detailing the early diagnosis of syphilitic optic atrophy.

Gummas of the Eyelid.—A review of literature by Cassady [92] reveals that the condition is uncommon. A case is presented which shows a resemblance to a chalazion.

Tonic Pupil.—Graveson [93] presents a well documented, intensive study of 15 cases of tonic pupil (Adie's syndrome). In discussing the diagnosis, Graveson states:

> Comparing these changes with what may be seen in the pupil in neurosyphilis there are several obvious points of similarity. In both the pupil may be irregular, it may be of any size, and it may show no response to light. Contraction of the pupil on convergence may be sluggish but when this happens in neurosyphilis the subsequent dilatation is normal, whereas in the tonic pupil it is always more delayed. This is the most important distinguishing feature and the surest way by which the two conditions may be differentiated by simple clinical examination.

Nonsyphilitic Interstitial Keratitis.—Cogan [94] describes four additional instances of the syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms. He described this symptom complex originally in 1945.[95] The ocular signs consisted of patchy granular infiltrates in the deep stroma, which varied from day to day and were unaccompanied with any conspicuous intraocular reaction. The vestibuloauditory symptoms were similar to those occurring in Ménière's disease and were followed by practically complete deafness in three of the patients, with complete recovery from the deafness in one. All patients were young adults, and all had leukocytosis.

Unusual Ocular Triad.—Rosen [96] reported on a patient showing embryonal cataract associated with interstitial keratitis and syphilitic choroiditis. This unusual triad had previously been reported on only two occasions.

Healed Syphilitic Neuroretinitis Papulosa.—Wolff [97] presented before the Chicago Ophthalmological Society on Nov. 15, 1948 a 28 year old woman with healed syphilitic neuroretinitis papulosa. This process developed one year after she had symptoms and signs of secondary syphilis. The ocular status has not changed, although her serologic reactions for syphilis became negative after antisyphilitic treatment.

Kestenbaum Capillary Number Test.—Kant [98] studied 125 eyes, 49 normal and 76 with atrophy, and counted the number of small vessels on the disk according to the

92. Cassady, J. V.: Gummas of the Eyelid, Am. J. Ophth. **33**:18-22 (Jan.) 1950.

93. Graveson, G. S.: The Tonic Pupil, J. Neurol., Neurosurg. & Psychiat. **12**:219-230 (Aug.) 1949.

94. Cogan, D. G.: Nonsyphilitic Interstitial Keratitis with Vestibuloauditory Symptoms, Arch. Ophth. **42**:42-49 (July) 1949.

95. Cogan, D. G.: Syndrome of Nonsyphilitic Interstitial Keratitis and Vestibuloauditory Symptoms, Arch. Ophth. **33**:144-149 (Feb.) 1945.

96. Rosen, E.: Embryonal Cataract Associated with Interstitial Keratitis and Syphilitic Choroiditis: Report of a Case, Arch. Ophth. **42**:749-754 (Dec.) 1949.

97. Wolff, P. G.: Healed Luetic Neuroretinitis Papulosa, Am. J. Ophth. **32**:1599 (Nov.) 1949.

98. Kant, A.: The Ophthalmoscopic Evaluation of Optic Atrophy, Am. J. Ophth. **32**:1479-1486 (Nov.) 1949.

Kestenbaum capillary number test. After graphing these results and correlating them with the visual acuity and areas of fields, he concluded that the capillary number test is a valuable adjunct in the diagnosis of optic atrophy and seems a reliable measure of the degree of atrophy present.

Syphilitic Primary Optic Atrophy: Early Diagnosis.—Klauder and Meyer [99] in a scholarly paper call attention to recent histological studies which demonstrate that syphilitic optic atrophy occurs in two forms: (1) an inflammatory form with secondary degeneration of the nerve fibers and (2) a primary degeneration in the form of tabetic atrophy of the nerve. They stress the necessity of an early ophthalmologic diagnosis, on the basis of a study of 397 patients with syphilitic primary optic nerve atrophy. Among the earliest symptoms of syphilitic optic nerve atrophy are the presence of neurosyphilis of silent course, impaired visual acuity, pain in the legs, diplopia and pupillary changes. These may be the only neurological abnormalities and may consist of inequality, irregularity, sluggishness in reaction to light, Argyll Robertson pupils and fixation to light and in accommodation. The presence of pupillary abnormalities calls for examination of the cerebrospinal fluid in order to exclude optic nerve atrophy. Treatment in the preatrophic stage in the cases reported by these authors prevented progress of the disease and preserved the visual acuity. It appears, therefore, that the problem of syphilitic optic nerve atrophy as a cause of blindness is concerned principally with early diagnosis. The ophthalmoscope and perimeter, according to these authors, are as essential as the spinal puncture needle in the diagnosis and management of syphilis and its complication, primary optic nerve atrophy.

In contrast to the preceding publication, a sketchy report, in which little actual detail is given, leads Igersheimer [100] to conclude that optic atrophy in tabes dorsalis and dementia paralytica has essentially the same pathogenesis.

CLINICAL MANIFESTATIONS OF CONGENITAL SYPHILIS

Nabarro [101] discusses the changing clinical manifestations and clinical course of congenital syphilis in the last 50 years. After many years of severe generalized types, there followed a period in which "a species of modified immunity or a communal resistance to the disease seemed to establish itself, so that the infantile lesions became less marked." At the time of World War I the treponeme seemed to have been reinvigorated, and many children died in spite of attempts at treatment with the new drugs, the arsphenamines. In the thirties, probably owing to the increasing use of the arsphenamine and heavy metal treatment and to the more prolonged administration of these drugs, the virulence of the treponeme again appeared to become less pronounced and cases of congenital syphilis became less conspicuous than formerly. Finally, the present penicillin era will modify the disease—but how this will occur depends on many more years of careful observation. While there have been great strides in the reduction of the incidence of congenital syphilis in England, its virtual extinction by the adequate examination and treatment of the expectant mother should be the aim. Nabarro suggests that penicillin-treated patients to be fol-

99. Klauder, J. V., and Meyer, G. P.: Early Diagnosis of Syphilitic Primary Optic Nerve Atrophy, Arch. Ophth. **43**:537-552 (March) 1950.

100. Igersheimer, J.: Atrophy of the Optic Nerve in Tabes and Dementia Paralytica, Arch. Ophth. **42**:170-177 (Aug.) 1949.

its virtual extinction by the adequate examination and treatment of the expectant (Sept.) 1949.

lowed up should include the following categories: (1) patients with primary or secondary acquired syphilis; (2) patients with acquired cardiovascular syphilis and neurosyphilis; (3) congenitally syphilitic infants in whom treatment was started at under 6 months of age; (4) congenitally syphilitic infants in whom treatment was over started at six months; (5) children with congenital neurosyphilis, and (6) children born after the mothers' antepartum treatment with penicillin alone.

FEVER THERAPY OF SYPHILIS

Continued interest in fever therapy is indicated by the studies of Noojin and his co-workers and others,[102] who have treated neurosyphilis with penicillin combined with fever.

Noojin, Pace and Pragtor [102a] treated 36 patients who had neurosyphilis or some form of ocular syphilis with fever. Fever was induced by means of two daily intravenous injections of typhoid vaccine. A second group of 20 patients was treated with three daily injections of typhoid vaccine. The three injection technic produced a reasonably satisfactory prolonged temperature elevation. The third injection increased the average total hours of fever 40 per cent over the two injection method. By utilization of the three injection technic, it was possible to produce 50 hours of temperature elevation to 102 F. or greater within an average of less than 13 days. According to the authors, no abnormal risk was involved in the three injection technic.

Heyman and Beeson [102b] observed the febrile response to typhoid bacterial pyrogen in a group of 85 patients with various diseases. The mean response elicited by patients with a variety of infections, such as pneumonia, hepatitis, typhus and tularemia, was the same as that observed in normal persons (the "normal" group was composed of febrile patients receiving penicillin for asymptomatic neurosyphilis). Patients with malaria, however, appeared to be comparatively resistant to the pyrogen. Patients with cirrhosis of the liver exhibited an exaggerated response.

PENICILLIN THERAPY OF SYPHILLIS

Mode of Action.—In spite of the intensive efforts to determine the mode of action of penicillin, little is actually known. We cite several recent reports probing this problem.

Eagle [103] believes that the therapeutic action of penicillin is determined in large part by the aggregate time the antibiotic remains at effective concentrations at the foci of infection. The absolute concentration is of little significance, provided only that it is in excess of the amount necessary to kill the organism at maximal rate. Increasing the concentration beyond the optimal effective level does not further accelerate the rate of death of the organism in vivo or in vitro. The aggregate time for which penicillin remains at bacterial levels is not the only factor which determines its therapeutic activity. When bacteria are being acted on by penicillin, some are

102. (*a*) Noojin, R. O.; Pace, B. F., and Pragtor, H. B.: Prolonged Fever Produced with 3 Injections of Typhoid Vaccine, Am. J. Syph., Gonor. & Ven. Dis. **34**:153-160 (March) 1950. (*b*) Heyman, A., and Beeson, P. B.: Influence of Various Disease States upon the Febrile Response to Intravenous Injection of Typhoid Bacterial Pyrogen, with Particular Reference to Malaria and Cirrhosis of the Liver, J. Lab. & Clin. Med. **34**:1400-1403 (Oct.) 1949.

103. Eagle, H.: The Mode of Action of Penicillin in Relation to Its Therapeutic Use, J. Mt. Sinai Hosp. **16**:109 (July-Aug.) 1949.

dying, the resistant organisms are not multiplying and infection is halted. Bacteria that are not killed become susceptible to the normal defense mechanisms of the body. Therefore, the rate of bacterial action in vivo is a composite of the direct effect of the drug itself and the action of the body's own defense mechanisms on the penicillin-damaged organisms. Organisms do not resume immediate multiplication after all the drug is excreted. Instead, two to four hours elapse before the bacteria recover sufficiently from the toxic effects to resume multiplication. At this time the organisms are relatively avirulent and susceptible to body defenses. Only after recovery of the toxic effects can the bacteria multiply and regain their resistance. The total duration of penicillin action is, therefore, the sum of the time the drug remains at effective levels at infectious foci plus the time required for the bacteria to recover and multiply. Even then, perhaps, several generations may multiply without significant increase in the total number before adverse effects arise. In the above circumstances aqueous penicillin providing effective levels in the tissues for only three to four hours may be safely used at eight hour intervals.

Previous studies by the Texas group were reported in the 1950 review.[1] In the present study Pratt and Dufrenoy [104] emphasize the blocking of mononucleotides in penicillin-sensitive organisms, concomitant with a shift toward the right of the -SH ⇌ S-S functions of the cell. It does not, however, give any explanation for the lack of toxicity of penicillin to man and other animals in which phosphorylated and sulfhydryl-containing compounds play such important roles. The experimental evidence shows that the ability of the organism to survive or even thrive in the presence of penicillin may be correlated with cytochemical ability to restore -SH groups fast enough for the respiratory systems to remain poised within the limits of reversible dehydrogenation, and that the organism may be assumed to be penicillin sensitive when penicillin stimulates dehydrogenation of its functional sulfhydryl groups faster than they can be restored. All the newly acquired evidence points toward a common specific functional unit as the sensitive locus in the cell. The degree of penicillin sensitivity may be a function of the ability of that functional unit to react to penicillin.

Mitchell,[105] in a concise report including convincing graphs, presents his observations on the mode of action of penicillin. He shows that a progressive disturbance of the balance of nucleotide and nucleic acid, accompanied with a change in composition of the nucleotide fraction, commences immediately after the addition of penicillin to the growing culture. This appears to be due to a net slowing of the rate of polymerization and not to a stimulation of synthesis from precursors. The nucleotide disturbance occurs simultaneously with, or is followed shortly by, an increase in the percentage by weight of total nucleic acid, owing to a slowing of the rate of formation of total cell mass relative to that of nucleic acid, the absolute rate of formation of nucleic acid being only slightly affected at this stage. The increase in the percentage of total nucleic acid is followed immediately by a somewhat rapid decrease toward a final low value similar to that found in normal old cells, the latter part of this process, if not also the earlier part, being accompanied with autolytic activity. The light-scattering power of the cells rises precipitately at about the time that the per-

104. Pratt, R., and Dufrenoy, J.: Recent Research on Penicillin Action, Texas Rep. Biol. & Med. **7**:180-219 (Summer) 1949.

105. Mitchell, P.: Some Observations on the Mode of Action of Penicillin, Nature, London, **164**:259-262 (Aug. 13) 1949.

centage of total nucleic acid reaches its peak, and it is thus evident that pronounced physical changes must take place at this point. The course of events is consistent with the view that the penicillin reacts initially with components involved in nucleotide dissimilation, and that the disturbance of nucleotide balance which follows in the growing cell leads immediately to other complex changes. Mitchell has no clear indication how the changes in the nucleotide fraction of the cells affect the glutamic acid accumulation mechanism, if there is any direct effect at all. But there seems little doubt that the glutamic acid accumulation mechanism is not affected until after the major changes in the nucleotide fraction have already taken place.

Production of a Constant Plasma Penicillin Level by Means of Daily Injections of Procaine Penicillin in Oil with Aluminum Monostearate.—Schaefer and Rashkoff [106] demonstrated that a constant penicillin plasma level greater than that attained with a single dose of any previously investigated preparation may be maintained by the daily administration of 300,000 units of procaine penicillin in oil with aluminum monostearate. Nineteen patients received 300,000 units intramuscularly each morning for three to six days. The average penicillin blood level increased from 0.16 unit per cubic centimeter on the first day to 0.48 unit on the fourth day, then remained stabilized in the 0.5 unit range.

Penicillin in Oil with Aluminum Monostearate: Blood Levels in Syphilis Therapy.—Taggart and his group [107] report their observations on the penicillin blood concentrations in 147 patients given varying doses of procaine penicillin G in oil with 2 per cent aluminum monostearate. The penicillin utilized in the study was from 87 certified lots from seven manufacturers. A micronized form (i. e., 95 per cent of the particles less than 5 microns in diameter) was contained in 35 of the lots tested. This was administered to 65 subjects. A nonmicronized form (particle size unspecified) was contained in 52 lots. This was administered to 85 subjects. Doses of 1,200,000, 1,500,000, 1,800,000, 2,400,000 and 3,000,000 units in one or two intragluteal repository sites were employed. Blood samples were withdrawn for assay regularly every 24 hours for 10 days and, in some instances, for as long as 20 days following injection. Blood penicillin concentrations were determined by the Bacillus subtilis method. In general, the micronized form tended to persist in the blood longer than the nonmicronized product. The method of administration (one or two intragluteal repository sites) did not have a significant effect on the peak or duration of the blood levels. The average serum concentrations for 2,400,000 and 1,800,000 units of the micronized product, using one deposit, were similar. The concentration for 1,500,000 units, while initially approximately one-half that for 2,400,000 and 1,800,000 units tended to be maintained for nearly the same length of time. Serums from 32 patients who showed penicillin levels on the tenth day were examined until they no longer showed measurable concentrations. Durations of measurable blood concentrations in these patients varied from 11 to 20 days. Jarisch-Herxheimer reactions were noted in 12 of the group of 97 patients with

106. Schaefer, L. E., and Rashkoff, I. A.: Production of a Constant Plasma Penicillin Level by Means of Daily Injections of Procaine Penicillin in Oil with Aluminum Monostearate, J. Mt. Sinai Hosp. **16**:300-302 (Jan.-Feb.) 1950.

107. Taggart, S. R.; Hendricks, F. D.; Chandler, V. L.; Welch, H.; Harley, D. H., and Olansky, S.: Penicillin in Oil with Aluminum Monostearate: Its Effect on Prolonged Blood Concentrations of Penicillin and a Preliminary Report of Its Use in the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:515-522 (Nov.) 1949.

primary and secondary syphilis. Possible sensitization phenomena were noted in two. Only 25 of the 97 patients were followed for six months. Of these 17 had negative serologic reactions, six had positive reactions and two were retreated, one with clinical and epidemiological evidence of reinfection and one with manifest clinical relapse.

Peacock and Gillespie [108] have demonstrated a striking difference in the duration of blood penicillin levels of bed patients and ambulant patients, which presumably is the result of the greater activity and blood flow of the gluteal muscles in the ambulant group. Following single injections of 2,000,000 units of procaine penicillin with 2 per cent aluminum monostearate, almost all the bed patients maintained blood penicillin levels in excess of 0.06 unit per cubic centimeter for six to seven days, and most of them for a longer time. In ambulant persons the effect was distinctly shorter, lasting for five days in about two thirds of the patients, but less than seven days in most of those tested.

Penicillin Concentration in Pregnant Rats and in the Rat Fetus.—Gabriel [109] experimented on penicillin concentrations in rats at various periods during pregnancy. The animals were given penicillin G in dosage comparable with human dosage. After 60, 90, 120 and 180 minutes, the animals were killed, and with sterile technics all organs of the mothers and fetuses were removed to be assayed for penicillin levels. Gabriel observed that the penicillin titer in animals is similar to that in man. After injection, the titer rises rapidly and falls rapidly. The lowest titer is reached in two to three hours after injection. In juices of organs the penicillin level is lower than in the blood. As time goes on, this value approaches blood levels. Most of the penicillin is excreted by the kidneys, which have a high concentration of the drug. In the second half of the pregnancy the placenta is moderately permeable to bacteriostatic levels (0.02 to 0.03 unit per cubic centimeter). The fetal organism contains bacteriostatic levels of penicillin, but as time progresses the levels drop more slowly. The placenta acts as a barrier to penicillin at the beginning of the pregnancy. Toward the end of the pregnancy the independence of fetal circulation does not affect the course of penicillin concentrations. Values for the amniotic fluid are similar to or identical with those for the fetal blood.

PRESENT DAY TREATMENT OF SYPHILIS

Gradually the best treatment for the various phases of syphilis is being evolved. In spite of the tendency for the picture to come to a sharper focus, there are still many differences of opinion in the various centers studying this problem. We cite, as samples of the various viewpoints, reports from New York,[110] from Ann Arbor,

108. Peacock, J. H., and Gillespie, W. A.: Procaine Penicillin with Aluminum Monostearate: Effects of a Single Large Dose in Bed and Ambulant Patients, Lancet **1**:495-497 (March 18) 1950.

109. Gabriel, H.: Ueber das Verhalten des Penicillintiters im mütterlichen und fötalen Organismus, Wien. klin. Wchnschr. **61**:886-890 (Dec. 16) 1949.

110. (*a*) Thomas, E. W.: Rapid Treatment of Syphilis with Penicillin: I. A Survey of the Problem, Bull. World Health Organ. **2**:233-248, 1949; (*b*) Modern Treatment of Syphilis, Including Syphilis of the Central Nervous System, Bull. New York Acad. Med. **25**:505-520 (Aug.) 1949. (*c*) Rosenthal, T.: Treatment of Syphilis in Private Practice, New York Med. **5**:16 (Sept. 5) 1949. (*d*) Webster, B.: Clinical Results of the Use of Penicillin in Syphilis, J. M. Soc. New Jersey **46**:380-386 (Aug.) 1949.

Mich.,[111] and from Philadelphia.[112] Efforts are still being made by various investigators toward the evaluation of a satisfactory ambulatory treatment for syphilis.[113]

Thomas [110a] believes that penicillin has proved superior to all other forms of antisyphilitic therapy both in safety and in therapeutic effectiveness. He states that in general 4,000,000 to 9,000,000 units of penicillin given over a 15 day period will accomplish as much in the treatment of all types of syphilis as any other known therapy. Since 1944 all patients with neurosyphilis at Bellevue Hospital, New York, have been treated with penicillin exclusively. The author stresses the fact that spinal fluid tests are the only reliable guides to evaluation of the syphilitic process and results of therapy.

Rosenthal [110c] recommends the following treatment schedules: For early syphilis procaine penicillin G is given in a total dosage of 6,000,000 units, in doses of 600,000 units (2 cc.) for 10 consecutive days, followed by two injections weekly for 10 weeks of oxophenarsine hydrochloride, together with or followed by administration of a bismuth preparation once a week for 10 injections. For neurosyphilis 9,000,000 units of procaine penicillin G is administered in doses of 600,000 units every other day for 15 injections. For late syphilis penicillin, oxophenarsine hydrochloride and a bismuth preparation are used. For infantile congenital syphilis penicillin G in aqueous solution is given every two to three hours around the clock in a total dosage of 100,000 to 400,000 units per kilogram of body weight over a period of eight to 15 days for children up to 2 years of age. Procaine penicillin G is administered in a daily dosage of 6,000 to 12,000 units per kilogram of body weight for two to three weeks to older infants and children. For syphilis in pregnancy the treatment is 600,000 units of procaine penicillin G for 10 days. Retreatment during each pregnancy is advised.

In a comprehensive review of the literature on the treatment of syphilis with penicillin, Webster [110d] places emphasis on the results obtained with various treatment schedules. There is some disagreement regarding the best method of treating central nervous system syphilis. The inflammatory forms are adequately treated with 4,200,000 units given over 14 days. Some workers are of the opinion that this schedule may be used in the treatment of tabes dorsalis and dementia paralytica. Others would rather use penicillin and malaria therapy for these.

According to Curtis,[111] of the University of Michigan, the addition of bismuth subsalicylate to the penicillin regimen does not increase the curative rate of penicillin alone. The addition of oxophenarsine hydrochloride to 1,200,000 units of penicillin gives a lower failure rate than penicillin administered alone but induces definite morbidity and mortality. Increased penicillin dosage might be equally effective. He suggests a variety of acceptable schedules with penicillin both alone and in com-

111. Curtis, A. C.: Modern Treatment of Syphilis, Postgrad. Med. **6**:22-33 (July) 1949.

112. Ingraham, N. R.: Intensive Therapy of Syphilis, Delaware State M. J. **21**:237-242 (Oct.) 1949.

113. (*a*) Scott, V.: Semiweekly Treatment of Syphilis with Procaine Penicillin in Oil: Reactions and Preliminary Results in 228 Patients, J. Lab. & Clin. Med. **34**:998-1006 (July) 1949. (*b*) Peabody, G. E., and Webster, B.: The Use of an Intermittent Ambulatory Schedule of Penicillin in Oil and Wax in the Treatment of Early Latent Syphilis and Syphilis in Pregnancy, New York State J. Med. **49**:1829-1830 (Aug. 1) 1949. (*c*) Magnuson, H. J.: Present Trends in the Treatment of Syphilis, North Carolina M. J. **10**:577-580 (Nov.) 1949. (*d*) Rausch, N. G.: Five-Day Ambulatory Penicillin Therapy of Early Syphilis, New York State J. Med. **49**:1668-1670 (July 15) 1949.

bination with oxophenarsine hydrochloride and/or a bismuth preparation. In early syphilis (656 patients) the earlier penicillin therapy is started, the greater the chance of cure, and the lower the quantitative serologic titer, the sooner the titer will decrease to near negativity. Most relapses occur at four months post treatment. Clinical cure is assured if the patient's serologic reaction becomes negative at the expected time and remains negative for a year.

In syphilis in pregnancy treated with penicillin sometime during the course of pregnancy, the infected woman has a 98 per cent chance of having a healthy, normal baby, as compared with a 17 per cent chance for untreated women, a 50 per cent chance with regimens of arsenical and bismuth treatment and an 85 per cent chance with massive arsenotherapy. In patients with central nervous system syphilis treated either with penicillin alone or with penicillin in the same dosage plus therapeutic malaria, from both the clinical and the spinal fluid standpoints it appears that, except for dementia paralytica and the tabetic form of dementia paralytica, the response to penicillin alone is as good as that to penicillin and malaria.

Ingraham,[112] of the University of Pennsylvania, concludes: "Penicillin is a most effective remedy for the treatment of syphilis and for most stages of the disease is the treatment of choice." Positive diagnosis of syphilis prior to treatment is necessary. Intramuscular injection is the preferred method of administration, and the maintenance of therapeutically effective blood levels throughout the course of treatment is essential. Satisfactory blood levels may be obtained by intramuscular injection of aqueous penicillin in doses of 40,000 to 50,000 units every two to three hours around the clock, or of 600,000 units of a delayed action penicillin preparation once daily. The treatment course should not be less than eight to 10 days. Arsenical, bismuth or fever therapy to supplement the initial course of penicillin administration is not recommended. Treatment courses, such as are used at the University of Pennsylvania, for the various types of syphilis are as follows: For symptomatic early syphilis 40,000 to 50,000 units of aqueous penicillin is given intramuscularly every two or three hours for 100 injections, or 600,000 units of a delayed action penicillin preparation is given intramuscularly daily for 10 injections. For latent syphilis the same dosage is used as for symptomatic early syphilis. Follow-up observation is made every six months to one year indefinitely for evidence of progression of the disease. In a syphilitic pregnant woman a single course of penicillin treatment at any time in the pregnancy protects the fetus in practically 100 per cent of cases. The dosage is that required for the stage of the disease presented by the patient, irrespective of pregnancy. In infantile congenital syphilis results are 100 per cent satisfactory if treatment is begun before the third month of life and 70 per cent satisfactory with treatment begun between 3 months and 2 years. For young and debilitated infants the dosage is 100,000 units of aqueous sodium penicillin per pound (0.5 Kg.) of body weight given intramuscularly in 120 divided doses every three hours over 15 days. For older infants a delayed action penicillin preparation may be given in a dosage of 150,000 to 300,000 units daily for 10 to 15 days. For active interstitial keratitis hospitalization is required, with fever therapy plus penicillin administration in a total dosage of 6,000,000 to 10,000,000 units over 15 days. Relapse occurs in approximately 30 per cent of cases. Hospitalization is also required in treatment of central nervous system syphilis, with 10,000,000 to 20,000,000 units of penicillin given for 10 to 20 days.

Scott [113a] essayed the evaluation of the therapeutic efficacy of procaine penicillin in oil administered semiweekly in the ambulant treatment of syphilis. He treated 228 patients with all stages of syphilis by this method. Although more prolonged observation is necessary for final evaluation, preliminary findings indicate that results with this regimen were comparable to those obtained with aqueous penicillin. No serious Jarisch-Herxheimer reactions were observed, and only 16 (7 per cent) of the patients failed to complete treatment, an indication of the superiority of penicillin therapy in case holding.

Treatment of Latent Syphilis and Syphilis in Pregnancy with Penicillin in Oil and Beeswax.—Sixty-one patients with early latent syphilis and 57 with maternal syphilis were treated by Peabody and Webster [113b] in the syphilis clinic of the New York Hospital, with an intermittent ambulatory regimen of 600,000 units of penicillin in oil and wax twice a week for six weeks. Bismuth salicylate in oil was given concurrently in a dosage of 0.2 Gm. once a week for 12 weeks. Patients were followed for six months or longer after treatment. Of the 61 patients with early latent syphilis, 53 (87 per cent) showed complete or partial seroreversal; the reactions of 38 (62 per cent) became totally serologically negative, while those of eight (13 per cent) remained positive. There were no relapses, infectious or serologic, after treatment. No syphilitic infants were born in the group of 57 patients with maternal syphilis.

Present Trends in Treatment of Syphilis.—According to Magnuson,[113c] present trends in the penicillin therapy of early syphilis are toward the development of ambulatory methods which permit patients to be treated by private physicians or in clinics rather than in hospitals. Studies on the treatment of syphilis with aqueous penicillin have demonstrated that adequate therapy for early syphilis may be provided by penicillin in a total dose of 2,400,000 to 4,800,000 units given in such manner as to provide adequate penicillin blood levels for more than 72 hours. Prolonging the duration of treatment appears to be advantageous, but increasing the total dose is apparently of little value. Equally satisfactory results have been obtained with penicillin in peanut oil and beeswax in a total dose of 2,400,000 to 4,800,000 units given over a period of four days to four weeks. Schedules using procaine penicillin in peanut oil with 2 per cent aluminum monostearate are being investigated. Doses of 300,000 units semiweekly, 600,000 units every third day for 15 days, 1,200,000 units weekly for two or four injections and even single injections of large doses have been reported to be efficacious. Since the use of prolonged action types of penicillin has made possible ambulatory treatment of early syphilis, it is expected that an increasing number of patients will be treated by the private physician. Magnuson emphasizes the physician's responsibility to cooperate with the public health services by reporting cases and contacts and in educating the patient.

In connection with this trend, Rausch [113d] treated 104 patients who had early acquired syphilis on an ambulatory basis with penicillin given on a five day treatment schedule (600,000 units of penicillin G in beeswax and peanut oil in a single daily injection for five days). Eighteen months' follow-up study of 84 cases shows results comparable to those in other favorable reports on longer treatment schedules.

(To Be Concluded)

News and Comment

GENERAL NEWS

Thirteenth International Congress of Military Medicine and Pharmacy.—The Thirteenth International Congress of Military Medicine and Pharmacy will be held in Paris from June 17 through 23, 1951. It will be open to physicians, pharmacists, dentists, veterinarians and officers of the administrative services in active service or in the reserve of the medical corps of any of the armed forces. The scientific papers presented at the Congress will deal with the following subjects: principles of organization of tactics and materials for emergency aid in case of mass influx of wounded after a major attack; organization of instruction of medical corps personnel; medical problems raised by air and submarine navigation; medical aspects of defense against atomic, biologic and chemical warfare, and present concepts of part played by the military pharmacist in war time. The registration fee is 2,000 francs for the members of the Congress and 1,000 francs per person for those accompanying the members. Requests for further information should be addressed to the Secrétariat Général du Congrès, Section Technique du Service de Santé, 8 bis Rue des Récollets, Paris 10, France.

The Hebrew Medical Journal.—The appearance of Volume 2, 1950 of *The Hebrew Medical Journal (Harofé Haivri)* concludes the twenty-third successful year of its publication under the editorship of Moses Einhorn, M.D. Written in Hebrew, with English summaries, the journal is a contribution to the development of the Hebrew medical literature. Among the articles of interest in volume 2 are "Surgical Treatment of the Painful, Stiff Hip (The Resection-Angulation Operation)" by Henry Milch, M.D., "Electroencephalography and the Epilepsies" by Samuel J. Lipnitzky, M.D., and an article by Dr. M. Temkin on the various infectious diseases, such as malaria, typhoid, pappataci and amebiasis, which prevailed in Palestine and have lately been checked by the Health Department of the Government of Israel. The editorial office of *The Hebrew Medical Journal* is located at 983 Park Avenue, New York 28.

PERSONAL NEWS

Appointment of Dr. David Nye Barrows.—Dr. David Nye Barrows, director of gynecology and medical executive officer at the New York Polyclinic Medical School and Hospital, has been made dean of the institution as of Jan. 1, 1951. Dr. Barrows also is clinical professor of gynecology and obstetrics at New York University College of Medicine.

Appointments to Editorial Staff of The American Journal of the Medical Sciences.—Dr. E. B. Krumbhaar has retired as editor of *The American Journal of the Medical Sciences* after 25 years' association with the journal. He will be succeeded by Dr. Richard A. Kern, professor and head of the Department of Medicine, Temple University School of Medicine, Philadelphia. Dr. Thomas M. Durant, professor of clinical medicine, Temple University School of Medicine, will be associate editor of the journal and Dr. Chris J. D. Zarafonetis, associate professor of internal medicine at Temple University, will be assistant editor.

SPECIAL NOTICE

For the general information of indexers, catalogers and library personnel with reference to the listing of the new title of this journal, we advise that the *Quarterly Cumulative Index Medicus* policy be followed. The *Quarterly Cumulative Index Medicus* with its volume 49 (January-June 1951) will list this journal under the new title, so that the letters A. M. A. will be included as an integral part of the title. For the completion of volume 48 (July-December 1950) the *Quarterly Cumulative Index Medicus* will continue to use the old title, without adding the designation A. M. A.

Book Reviews

Veterans Administration Technical Bulletins, Series 10, Volume 3. Pp. 60. Veterans Administration, Government Printing Office, Washington 25, D. C., 1949.

Here one finds bound under one cover Technical Bulletins 40 to 60 from the Veterans Administrative Series 10. The subjects are unrelated, including such matters as spotted fever, radioisotopes and the biologic aspects of pernicious anemia. The authors are all authorities in their field, and these bulletins summarize in excellent fashion up-to-date knowledge on the various subjects.

Recent Advances in Chemotherapy. Volume I. Third edition. By G. M. Findlay, C.B.E., Sc.D., M.D., F.R.C.P. Price, $7.50. Pp. 625. The Blakiston Company (Division of Doubleday & Co., Inc.), 1012 Walnut St., Philadelphia 5, 1950.

This compact volume is the first of four dealing with recent advances in chemotherapy. Chemotherapy of diseases due to insects, helminthic infections, amebiasis and protozoal infections in general, leishmaniasis and trypanosomiasis is discussed. The matter seems up to date and critically presented; there are bibliographies and tables.

Annual Review of Physiology. Volume 12. By various authors. Edited by Victor E. Hall. Price, $6. Pp. 609. Annual Reviews, Inc., and the American Physiological Society, Stanford, Calif., 1950.

This review is organized in the same fashion as the previous ones and, like them, is good. The authors of the various sections have summarized well the papers published on the respective subjects. This book should prove to be of value not only to physiologists but also to students, internists and others interested in the mechanism of disease. The detailed author and subject index makes the volume extremely valuable for reference.

Transactions of the Tenth and Eleventh Conferences on Problems of Aging, Feb. 9-10, 1948 and April 25-26, 1949. By various authors. Edited by Nathan W. Shock. Price, $3.75. Pp. 258. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1950.

This is a compilation of the various papers presented at the conferences on aging arranged by the Josiah Macy, Jr., Foundation. The participants include persons interested in medical problems related to aging, but many of them are not gerontologists in the strict sense. Such subjects as regeneration of the liver in old age, sexual regeneration in elderly women, problems encountered in an old age counseling center, problems associated with age of retirement and nutritional factors are among those discussed. This book should be useful to those interested in the problem of aging. The discussions on the animal studies are better than those on studies concerned with man.

Progress Volume: Modern Developments in Therapeutics and Methods of Treatment, to Accompany "An Integrated Practice of Medicine." By Harold Thomas Hyman, M.D. Price, $10. Pp. 867. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1950.

This progress volume is full of useful information. Many tables summarize a large amount of material and are a good source of information when there is little time to search elsewhere. In the first part of the volume the various antigens used in diagnosis are listed, and one learns where one can obtain such skin testing agents as coccidioidin, which as yet is commercially unavailable. The therapeutic usefulness of aureomycin, chloramphenicol (chloromycetin®) and terramycin is well summarized, but, of course, individual observations do differ. The author places chloramphenicol ahead of a combination of streptomycin and sulfonamides in the treatment of Bacillus pyocyaneus infections.

In addition, there is a large quantity of useful laboratory material relative to the employment of various therapeutic agents. For example, the various methods of determining the coagulation

time and the prothrombin time are outlined in a discussion on bishydroxycoumarin (dicumarol®) and heparin therapy.

Such volumes have one great disadvantage, which is that they are soon outdated and must be revised almost twice yearly. In the present volume, for example, penicillin is listed as the antibiotic of choice in therapy of actinomycosis. Already, before this book is even off the presses, there are reports of chloramphenicol being exceptionally effective in treatment of this infection. All in all, however, this is a very well written, accurate and useful volume.

The Nose: An Experimental Study of Reactions Within the Nose in Human Subjects During Varying Life Experiences. By Thomas H. Holmes, M.D., Helen Goodell, B.S., Stewart Wolf, M.D., and Harold G. Wolff, M.D. First edition. Price, $4.50. Pp. 154, with 37 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1949.

This small book briefly describes the reactions of the nasal mucosa, especially of the turbinate bodies, to psychic disturbances. The reactions were found to be similar in general nature to responses in the gastric mucosa. These studies are examples of the somatic reactions to psychic stimuli which have interested the authors. Although many of the reactions are probably known to most readers, this monograph correlates them.

There are several aspects of the book which are not clearly presented. For example, the authors state on page 1 that the nasal structures supply 2 quarts (1.9 L.) of water. This should be clarified, since insensible water loss does not exceed 1,000 Gm. daily. On page 32 it is stated that chilling of the body can occur without "physical contact." Such minor erroneous statements are of little importance, however. This monograph should interest many in the fields of psychiatry and psychology.

Proceedings of the First Clinical ACTH Conference. Edited by John R. Mote. Price, $5.50. Pp. 608, with 414 illustrations. The Blakiston Company (Division of Doubleday & Co., Inc.), 1012 Walnut St., Philadelphia 5, 1950.

In October 1949 Armour & Co., of Chicago, called a conference of the medical research teams investigating the clinical effects of pituitary adrenocorticotropic hormone (ACTH). This book is a compendium of the reports made at that meeting. It is gratifying that such a large volume of experimental data produced by reliable investigators has been made available to the medical profession before ACTH was released for general distribution. This book is a "must" for researchers in the adrenal steroid field and should be read by all practitioners before they administer ACTH to their patients.

The physiological changes induced by ACTH administration are fully covered, along with its effect in various disease states, such as neoplastic diseases, hyperthyroidism, gout, hypertension, nephritis, leukemia, rheumatoid arthritis, rheumatic fever and other collagen diseases, ulcerative colitis, allergic diseases, chronic hepatic disease, various infections, neuropsychiatric states, alcoholism, myasthenia gravis and other neurological disorders.

The findings reported will emphasize the necessity of keeping patients being treated with ACTH under strict supervision so that prolonged negative nitrogen balance, retention of sodium, hyperglycemia, potassium deficiency, adrenal exhaustion and other untoward effects will not supervene.

The papers indicate that all the so-called collagen diseases, rheumatoid arthritis, skin and ocular disorders associated with allergy are beneficially affected by ACTH. On the other hand, in the treatment of acute and chronic infections, while a drop in temperature and amelioration of symptoms often occurred, the growth of bacteria was unaffected.

All those interested in the wide field opened up by the availability of the adrenal steroids and ACTH will find this an exciting and instructive book.

Progress in Clinical Endocrinology. Edited by Samuel Soskin, M.D. $10. Pp. 641, with 35 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1950.

This excellent book under the editorship of Samuel Soskin is not a textbook of endocrinology in the strict sense. It is an attempt to correlate newer developments in the endocrinological field by experts doing active investigation in the areas which they are discussing. In all,

91 authors collaborated in this unusual volume. Although much new knowledge has been gained about pituitary-adrenal relationships and adrenal cortex steroids by clinical trials of pituitary adrenocorticotropic hormone (ACTH) and cortisone since this volume left the presses, the fundamental knowledge here presented is in no way outdated. In fact, the clinical results now being reported could all have been predicted from the data given here.

The busy internist will find some chapters hard going, for the material is in no way diluted for spoon feeding. But if he does get through the excellent reviews on thyroid dysfunction and its management and the discussions on the pituitary and adrenal glands he will be much better equipped to use the interesting new tools now available to him for therapy in these fields. The sections on the gonads, pancreas and parathyroids are of equal interest. Dr. Soskin and his associates have done a remarkably good job of bringing a difficult and rapidly changing field of knowledge up to date in a most satisfactory manner.

Principles of Internal Medicine. By T. R. Harrison, M.D. Price, $12. Pp. 1,590, with 245 illustrations. The Blakiston Company (Division of Doubleday & Co., Inc.), 1012 Walnut St., Philadelphia 5, 1950.

This is an excellent textbook and an important addition to any physician's library. The style of presentation is new and progressive. The contributors are adequately qualified.

Briefly, this book is divided into seven sections. After an introductory paragraph about the taking of the history, the physical examination, the relative importance of the laboratory and technical aids and the management of the patient, there is a general discussion of the cardinal manifestations of disease, including a thorough review of pain and its localization, weakness, dyspnea, jaundice and urinary symptoms. In the next part, much space is given to a consideration of basic physiological principles.

The remainder of the book is devoted to disease entities considered under the headings of reactions to stress and antigens, metabolic and endocrine disorders, disorders due to chemical and physical agents, diseases due to biologic agents and diseases of organ systems.

There is much useful information here with little extra padding. The sections on electrophysiology of heart muscle, electrolyte balance and intermediary metabolism are well done. Rarer diseases, of course, receive less complete consideration, and this would hardly be the book from which to learn all about a process such as Hand-Schüller-Christian disease. There is a good section on congenital heart disease and cardiac catheterization studies. There is some departure from well accepted ideas, such as the consideration of acute tonsillitis, pharyngitis and scarlet fever all under the same heading. Vincent's angina is mentioned in the differential diagnosis of acute tonsillitis, but there is no formal discussion of this condition elsewhere in the book.

In conclusion, one must say that this is a valuable, important book crammed full of useful information and so styled as to make it easy to dig out.

Aphorisms of Sir William Osler: From His Bedside Teachings and Writings. Collected by Robert Bennett Bean; edited by William Bennett Bean, M.D. Price, $2.50. Pp. 159. Henry Schuman, Inc., Publishers, 20 E. 70th St., New York 21, 1950.

Now that the surviving ranks of Osler's students are running very thin, there seems to be a last minute effort to recapture in some concrete form the legendary atmosphere of his clinic. Dr. Joseph Pratt's recent book, "A Year with Osler," succeeds well in this attempt, and now comes a little volume of aphorisms from Osler's bedside teachings and writings collected with loving care by the late Dr. Robert Bennett Bean. Osler was a great man, and above all he had a stirring personality; there is no doubt about the impact of his conversation and teaching on his associates. The world has changed much, however, since that wonderful era of the late nineties, and, alas, many of these aphorisms now seem obvious, if not naïve. None the less, there are in this little book sound counsel, wise philosophy which never grows old and, above all, the ring of true idealism, refreshing in an era when promotion has all but made a joke of sincerity. "Medicine is learned at the bedside and not in the classroom." "Medicine is a science of uncertainty and an art of probability." "The physiognomy of disease is learned slowly." Every medical student and young doctor should have this compendium at his bedside.

The Year Book of Medicine, 1950. Edited by Paul B. Beeson and others. Price, $5. Pp. 819, with many illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1950.

The latest "Year Book of Medicine" contains the selections of the editors in their respective fields of infectious diseases, diseases of the chest, diseases of the blood and blood-forming organs, diseases of the heart, blood vessels and kidney and diseases of the digestive system. The period May 1949 to May 1950 is covered. As in past years, the selection of material is, for the most part, excellent and the frank comments of the reviewers add much to the value of the abstracts. For the busy internist anxious to keep abreast of new developments, this collection of pertinent, informative articles representing the fields enumerated should be a real boon.

Louis Pasteur, Free Lance of Science. By René J. Dubos. Price, $5. Pp. 418, with 12 illustrations. Little, Brown & Co., 34 Beacon St., Boston 6, 1950.

In this magnificent biography of medicine's most illustrious investigator, Dr. René J. Dubos has recreated the Pasteur legend in a way that should make the spine of every student of the art tingle. By his penetrating analysis of the problems of the last half of the nineteenth century and of the steps by which Pasteur moved from one important phase of his investigations to the next, piling triumph on triumph, Dubos has added to his own scientific and literary stature.

Beginning with the discovery, at the age of 26, of the relation between the crystal morphology of organic solids and their ability to rotate the plane of polarized light, Pasteur was led into a study of the mechanisms of fermentation. It was during his investigations in this perplexing field that micro-organisms claimed his interest, and he was led to the important concept of the life of certain of these "microbes" without the presence of oxygen as the fundamental mechanism of the fermentative process. Shortly thereafter, a call for his genius in solving the problems of the silk industry resulted in his discovery of microbial life —both a virus and a bacterium—as the chief cause of silkworm disease. Chicken cholera, anthrax and rabies then claimed his attention.

In this absorbing narrative one journeys with Pasteur to the vineyards and breweries, where he personally supervised the translation of his laboratory experiments into commercial processes which transformed the whole industry; into the silkworm nurseries, where his new technics for selection of noninfected eggs rescued this devastated industry from extinction; into the fields, where his large open-air experiments demonstrated the value of immunization against anthrax to all who would come and see; into the clinic, where injections of his "attenuated" virus protected against rabies. Always the champion of applied science, he saw every discovery through to its application in improving the lot of man. The amazing scope of these observations and their consequences are amply covered in Dubos' book, and the text is frequently enriched by quotations from Pasteur's prolific writings, such as the following:

"Preconceived ideas are like searchlights which illumine the path of the experimenter and serve him as a guide to interrogate nature. They become a danger only if he transforms them into fixed ideas. This is why I should like to see these profound words inscribed on the threshold of all the temples of science: 'The greatest derangement of the mind is to believe in something because one wishes it to be so.'"

At a time that bookstalls are glutted with dull and superficial matter, it is a satisfaction to recommend this thoroughly delightful and authentic account of one of medicine's great heroes to physicians, their students and their patients.

Clinical Examination of Patients, with Notes on Laboratory Diagnosis. By John Forbes and W. N. Mann. Price, $4.50. Pp. 323, with 60 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1950.

This book is designed primarily for the student during his introduction to clinical medicine. Beginning with a section on the art of history taking, the chapters cover the examination of the body in a systemic fashion and discuss the significance of the various physical findings in a brief but adequate manner. Auxiliary diagnostic aids, such as roentgenologic and laboratory procedures that are pertinent to the system are described in each chapter with appropriate

illustrations. The authors have succeeded in presenting all aspects of the clinical examination, while at the same time maintaining the proper emphasis on the bedside examination. Especially noteworthy is the chapter on the examination of the central nervous system, in which diagrams and summaries are used freely to emphasize neurological findings and their significance. Six color plates illustrate the commoner findings in examination of the retina. The concluding chapter is devoted to detailed methods of performing the simpler laboratory tests; a brief discussion of the more elaborate laboratory investigations is given.

This book may be recommended to the student entering the clinical years and also to interns, residents and practicing clinicians as an aid to increasing their diagnostic acumen.

Symposia on Nutrition: Plasma Proteins, volume 2. Edited by John B. Youmans, M.D. Price, $6.50. Pp. 370, with 116 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1950.

This finely printed and illustrated book includes a series of papers presented at a symposium on nutrition sponsored by the Robert Gould Research Foundation, Inc., Cincinnati. The 17 articles, some of which assume almost monographic size, were written by a series of recognized authorities in the field. They deal with physical, chemical, physiological and clinical problems connected with the blood proteins. The book should be of special interest to clinicians, since it bridges the gap between laboratory and clinic.

The Antihistamines. By Samuel M. Feinberg, S. Malkiel and A. R. Feinberg. Price, $4. Pp. 291, with 27 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1950.

The stated purpose of the authors is to condense the facts, crystallize the essence and present the practical application of our knowledge of the antihistamines. In the section on experimental studies they consider the role histamine plays in anaphylaxis and allergy; while the histamine theory is tenable only as a partial explanation, there can be little doubt that histamine is involved in these conditions. Histamine manifestations can be controlled by means of one or more of the following sequences: (1) preventing the antibody-antigen union; (2) modifying the action of liberated histamine by drugs which have a reversing action (epinephrine); (3) inactivating the histamine (histaminase); (4) desensitizing the tissues against the action of histamine by graded doses of histamine itself; (5) blocking the action of histamine by compounds which unite with or compete for histamine or which fix themselves on the effector cells and so inhibit the action of histamine; (6) preventing the formation or release of histamine (antihistaminogenesis).

The second section of the book concerns itself with clinical observations. Of all the allergic respiratory manifestations, seasonal hay fever has responded best to the antihistamines. The asthma associated with hay fever is not prevented appreciably by the antihistamines; frank asthma in general is virtually unresponsive to these drugs. Probably the most important and one of the most constant effects of the drugs on lesions of the skin is the antipruritic action. Urticaria has been relieved to a greater extent by these drugs than has any other disease, acute urticaria being more responsive than chronic. Morbilliform, erythematous and similar itching rashes often due to drugs respond favorably to the antihistamines. The antihistamines will benefit most patients with serum sickness syndrome.

A chapter is devoted to the use of antihistamines in miscellaneous conditions; the use of these drugs in the common cold is particularly skilfully handled. The authors believe the only action of the antihistamines in the common cold is reduction of some of the secretions and perhaps the sneezing. For such effects full doses are required, and even then this action is obtainable only in a minority of patients. These drugs by their central action on the vomiting center affect favorably conditions associated with nausea, including motion sickness and nausea and vomiting of pregnancy. Chapters are devoted to administration and dosage, as well as the toxic effects of these agents. There are an excellent bibliography and a good index. The authors have succeeded well in their aims, and this small book can be recommended without reservation.

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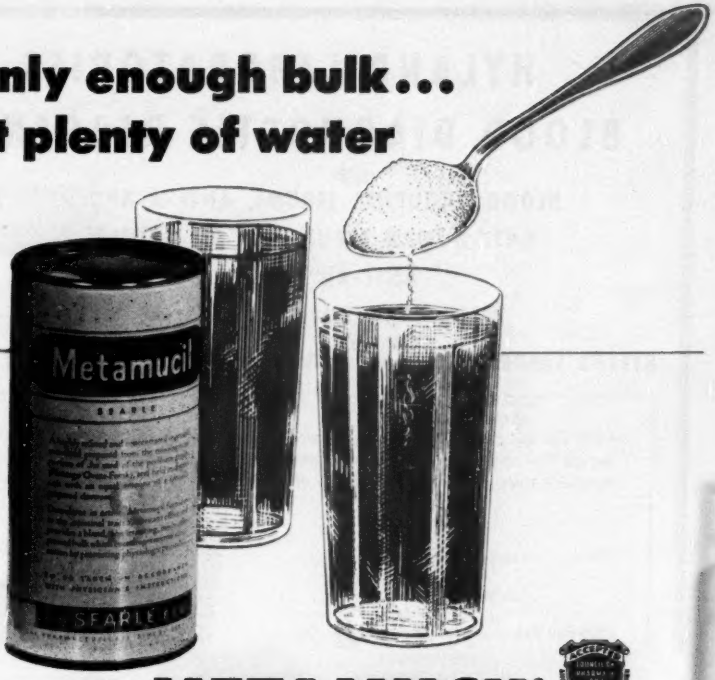

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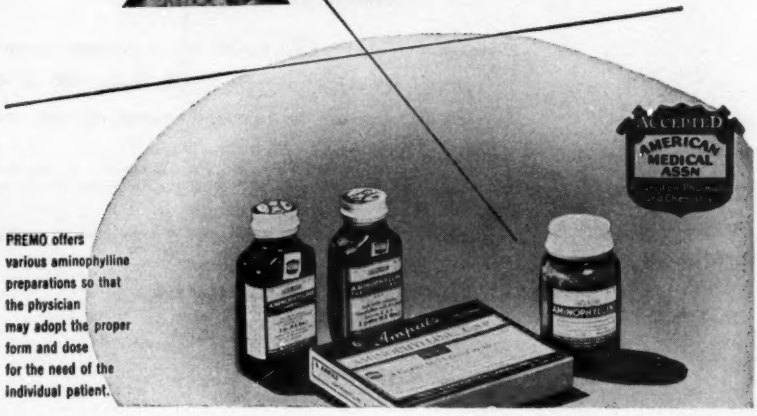

PREMO offers various aminophylline preparations so that the physician may adopt the proper form and dose for the need of the individual patient.

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"...it was found that the characteristic activity of globin insulin and 2:1 mixture (of protamine zinc and regular) insulin is essentially the same."[1]

"Not often do either globin insulin or a 2:1 mixture require supplementary use of regular insulin. Fully 80% of all severe diabetics can be balanced satisfactorily with one of them."[2]

1. *Roeb, B. B., Rohr, J. H., and Colwell, A. R.: Proc. House Staff Dept. Med., Wesley Memorial Hospital, Chicago, Ill. Feb. 6, 1948.*

2. *Rohr, J. H., and Colwell, A. R., Proc. Amer. Diabetes Assn. 8:37, 1942.*

COMPLETE CLINICAL INFORMATION WILL BE SENT ON REQUEST

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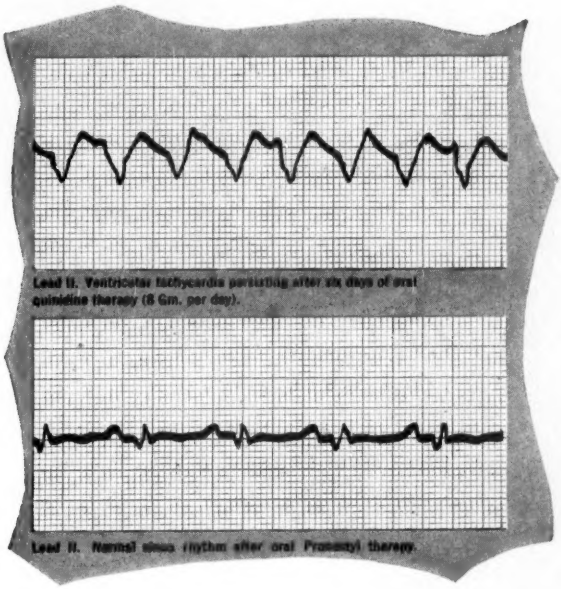
PRONESTYL *Hydrochloride*

Squibb Procaine Amide Hydrochloride



Lead II. Ventricular tachycardia persisting after six days of oral quinidine therapy (8 Gm. per day).

Lead II. Normal sinus rhythm after oral Pronestyl therapy.

Oral administration of Pronestyl in doses of 3-6 grams per day, for periods of time varying from 2 days to 3 months, produced no toxic effects as evidenced by studies of blood count, urine, liver function, blood pressure, and electrocardiogram. Pronestyl may be given intravenously with relative safety.

PRONESTYL IS A TRADEMARK OF E. R. SQUIBB & SONS

Pronestyl Hydrochloride Capsules, 0.25 Gm., bottles of 100 and 1000.
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Yes, the fact is that a bacterial census following therapeutic doses of SULFASUXIDINE® succinylsulfathiazole will show a rapid reduction of *E. coli* organisms from 10,000,000 to less than 1,000 per gram of wet stool.

Sulfasuxidine

succinylsulfathiazole

SHARP & DOHME

SULFASUXIDINE is specifically indicated as a safeguard against peritonitis before and after intestinal surgery, and is particularly valuable prophylactically in radical procedures.[1] It has also proved effective for control of ulcerative colitis and *E. coli* infections of the genitourinary tract,[2] and is considered a drug of choice in treatment of acute or chronic bacillary dysentery, including carrier states of this disease.[3] Toxic reactions are negligible, since 95% of the dose remains in the gastrointestinal tract.
Supplied in 0.5-Gm. tablets, bottles of 100, 500, and 1,000; powder in ¼ and 1 lb. bottles.
Sharp & Dohme, Philadelphia 1, Pa.

1. Internat. Abstr. Surg. *83*:1, July 1946.
2. Am. J. Obst. & Gynec. *49*:114, Jan. 1945.
3. J.A.M.A. *128*:1152, Aug. 18, 1945.